



PHD

## Sequential Processes Involving Catalytic C-H Functionalisation

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# **Sequential Processes Involving Catalytic C-H Functionalisation**

William R. Reynolds

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry and

Centre for Sustainable Chemical Technologies

December 2013

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## Abstract

The work described herein involves the exploration of sequential reaction processes involving catalytic C-H functionalisations and Pd-catalysed cross-couplings in both batch and continuous-flow operation, in an effort to improve overall reaction efficiencies.

Chapter 1 introduces the concept of sequential reaction processes, particularly catalytic C-H functionalisation strategies and how these can be combined in an iterative fashion, as well as in conjunction with other synthetic transformations, to reduce waste and improve the overall efficiency of synthetic processes with a view to providing cleaner and more sustainable synthetic routes to useful molecular architectures.

Chapter 2 focuses on efforts to widen the scope of a Ru-catalysed *meta*-selective C-H bond functionalisation protocol in an effort to increase its synthetic utility, along with an investigation into previously unseen dimeric byproducts formed during the reaction.

Chapter 3 details work on the development of a sequential chelation-assisted aromatic C-H functionalisation strategy, via a *meta* then *ortho* functionalisation sequence, for the synthesis of highly substituted 2-phenylpyridine derivatives, with exploration of the scope of the methodology.

Chapter 4 explores the synthesis and characterisation of novel dimeric 2-arylpyridine species using a sequential Suzuki coupling/cross-dehydrogenative coupling protocol, as well as their potential to act as novel bidentate ligands.

Chapter 5 introduces the use of continuous-flow processes within organic synthesis and provides an overview of Pd-catalysed cross-coupling reactions conducted within continuous-flow systems.

Chapter 6 outlines a synthetic strategy for conducting sequential cross-coupling/C-H functionalisation processes in flow, in an effort to develop fast and efficient methodologies for the synthesis of highly substituted 2-phenylpyridines.

Chapter 7 provides experimental details and characterisation data for compounds discussed in the previous chapters.

# Contents

|                         |           |
|-------------------------|-----------|
| <b>Abbreviations</b>    | <b>11</b> |
| <b>Acknowledgements</b> | <b>13</b> |

---

|                        |           |
|------------------------|-----------|
| <b>1. Introduction</b> | <b>15</b> |
|------------------------|-----------|

---

|            |   |           |
|------------|---|-----------|
| <b>1.1</b> | <b>Green Chemistry and Sustainability</b>                   | <b>15</b> |
| -          | 1.1.1 The 12 Principles of Green Chemistry                  | 16        |
| -          | 1.1.2 Sustainability  | 16        |
| -          | 1.1.3 E Factors and Pharmaceuticals                         | 17        |
| <b>1.2</b> | <b>Catalytic C-H Functionalisation</b>                      | <b>19</b> |
| -          | 1.2.1 Sequential C-H Functionalisations                     | 21        |
| -          | 1.2.2 Sequential C-H Functionalisation/Cross-coupling       | 27        |
| -          | 1.2.3 Sequential C-H Functionalisation/Other Transformation | 30        |
| -          | 1.2.4 Directing Group Modifications                         | 32        |
| <b>1.3</b> | <b>Summary</b>  | <b>36</b> |

---

|   |           |
|---|-----------|
| <b>2. Expanding the Scope of Ru-catalysed <i>meta</i> C-H Functionalisation</b> | <b>38</b> |
|---|-----------|

---

|            |  |           |
|------------|--|-----------|
| <b>2.1</b> | <b><i>meta</i>-Selective Aromatic C-H Functionalisations</b> | <b>38</b> |
| <b>2.2</b> | <b>Alternative Directing Groups</b>                          | <b>42</b> |
| <b>2.3</b> | <b>Experimental Design</b>                                   | <b>43</b> |
| <b>2.4</b> | <b>Dimeric Byproducts</b>                                    | <b>45</b> |

|            |                    |           |
|------------|--------------------|-----------|
| <b>2.4</b> | <b>Conclusions</b> | <b>48</b> |
|------------|--------------------|-----------|

---

|   |           |
|---|-----------|
| <b>3. Sequential C-H Functionalisation of 2-Phenylpyridines</b> | <b>49</b> |
|---|-----------|

---

|            |  |           |
|------------|--|-----------|
| <b>3.1</b> | <b>Complementary Regioselectivity</b>    | <b>49</b> |
| <b>3.2</b> | <b>Reaction Pathway 1</b>                | <b>50</b> |
| -          | 3.2.1 <i>ortho</i> C-H functionalisation | 50        |
| -          | 2.2.2 <i>meta</i> C-H functionalisation  | 52        |
| <b>3.3</b> | <b>Reaction Pathway 2</b>                | <b>54</b> |
| -          | 3.3.1 <i>meta</i> C-H functionalisation  | 54        |
| -          | 3.3.2 <i>ortho</i> C-H functionalisation | 55        |
| -          | 3.3.3 <i>Bromination substrate scope</i> | 58        |
| -          | 3.3.4 <i>Further functionalisation</i>   | 59        |
| <b>3.4</b> | <b>Conclusions</b>                       | <b>59</b> |

---

|   |           |
|---|-----------|
| <b>4. Synthesis and Properties of Novel 2-Arylpyridine Dimers</b> | <b>60</b> |
|---|-----------|

---

|            |   |           |
|------------|---|-----------|
| <b>4.1</b> | <b>Chelation-assisted Oxidative Homocoupling</b>                      | <b>60</b> |
| <b>4.2</b> | <b>Synthesis of 2-arylpyridines via Suzuki Coupling</b>               | <b>62</b> |
| -          | 4.2.1 Dioxaborinanes  | 62        |
| -          | 4.2.2 Suzuki coupling   | 63        |
| <b>4.3</b> | <b>Oxidative Homocoupling of 2-arylpyridines</b>                      | <b>64</b> |
| -          | 4.3.1 Characterisation of 2-(naphthalen-1-yl)pyridine dimer           | 65        |
| -          | 4.3.1.1 Colour generation   | 66        |
| -          | 4.3.1.2 Variable temperature <sup>1</sup> H NMR spectroscopic studies | 69        |

|            |   |           |
|------------|---|-----------|
| -          | 4.3.1.3 Atropisomerism                                  | 70        |
| <b>4.4</b> | <b>Preparation of Transition Metal Complexes</b>        | <b>71</b> |
| <b>4.5</b> | <b>Conclusions</b>                                      | <b>73</b> |
| <hr/>      |   |           |
|            | <b>5. Coupling Reactions in Continuous-flow Systems</b> | <b>74</b> |
| <hr/>      |   |           |
| <b>5.1</b> | <b>Introduction</b>                                     | <b>74</b> |
| <b>5.2</b> | <b>Coupling Reactions in Flow</b>                       | <b>75</b> |
| -          | 5.2.1 Suzuki-Miyaura coupling                           | 75        |
| -          | 5.2.2 Mizoroki-Heck coupling                            | 78        |
| -          | 5.2.3 Sonogashira coupling                              | 80        |
| -          | 5.2.4 Murahashi coupling                                | 82        |
| -          | 5.2.5 Hiyama coupling                                   | 84        |
| -          | 5.2.6 Carbonylative couplings                           | 84        |
| -          | 5.2.7 Buchwald-Hartwig amination                        | 86        |
| <b>5.3</b> | <b>Palladium Catalysts for Flow Systems</b>             | <b>88</b> |
| -          | 5.3.1 Heterogeneous supported catalysts                 | 88        |
| -          | 5.3.1.1 Palladium on charcoal                           | 88        |
| -          | 5.3.1.2 Pd EnCat  | 90        |
| -          | 5.3.1.3 Silicon dioxide supports                        | 93        |
| -          | 5.3.1.4 Polymeric supports                              | 94        |
| -          | 5.3.1.5 Magnetic nanoparticles                          | 95        |
| -          | 5.3.1.6 Monolithic supports                             | 97        |
| -          | 5.3.2 Homogeneous Catalysts                             | 100       |
| -          | 5.3.2.1 Single-phase reactions                          | 100       |
| -          | 5.3.2.2 Biphasic systems                                | 102       |

|            |  |            |
|------------|--|------------|
| <b>5.4</b> | <b>Continuous-flow Technologies for Cross-coupling</b>     | <b>104</b> |
| -          | 5.4.1 Microreactors  | 104        |
| -          | 5.4.2 Microwave-assisted continuous-flow organic synthesis | 105        |
| -          | 5.4.3 Towards sequential coupling reactions in flow        | 107        |
| <b>5.5</b> | <b>Summary</b>   | <b>108</b> |

---

|  |            |
|--|------------|
| <b>6. Sequential C-X and C-H Bond Functionalisations in Flow</b> | <b>110</b> |
|--|------------|

---

|            |   |            |
|------------|---|------------|
| <b>6.1</b> | <b>Blueprint for a Sequential Flow Protocol</b> | <b>110</b> |
| <b>6.2</b> | <b>Cross-coupling in Flow</b>                   | <b>111</b> |
| -          | 6.2.1 Dioxaborinanes in flow                    | 112        |
| -          | 6.2.2 Boronic acids in flow                     | 114        |
| -          | 6.2.3 ICP-MS leaching studies                   | 116        |
| <b>6.3</b> | <b>C-H Functionalisation in Flow</b>            | <b>118</b> |
| -          | 6.3.1 <i>meta</i> sulfonation                   | 118        |
| -          | 6.3.2 Hydroxylation                             | 119        |
| -          | 6.3.2 Oxidative homocoupling                    | 119        |
| <b>6.4</b> | <b>Conclusions</b>                              | <b>122</b> |

---

|                        |            |
|------------------------|------------|
| <b>7. Experimental</b> | <b>123</b> |
|------------------------|------------|

---



---

|                      |            |
|----------------------|------------|
| <b>8. References</b> | <b>192</b> |
|----------------------|------------|

---

## **Appendices**

|                                      |     |
|--------------------------------------|-----|
| - Appendix 1 – Crystallographic data | 197 |
| - Appendix 2 – Publications          | 222 |

## Abbreviations

|                   |  |
|-------------------|--|
| Ac                | Acetate  |
| Ad                | Adamantane   |
| acac              | Acetylacetone  |
| BiPy              | 2,2'-bipyridyl   |
| BINAP             | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl  |
| BMIm              | 1-Butyl-3-methylimidazolium  |
| Bn                | Benzyl   |
| Boc               | Di- <i>tert</i> -butyl dicarbonate   |
| BQ                | Benzoquinone   |
| BrettPhos         | 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenylBu <i>n</i> -Butyl |
| Bz                | Benzoyl  |
| CDCl <sub>3</sub> | Deuterated chloroform  |
| COD               | 1,5-Cyclooctadiene   |
| CPME              | Cyclopentylmethylether   |
| Cy                | Cyclohexyl   |
| DABCO             | 1,4-Diazobicyclo(2.2.2)octane  |
| DBA               | Dibenzylideneacetone   |
| DCE               | 1,2-Dichloroethane   |
| DCPE              | 1,2-Bis(dicyclohexylphosphino)ethane   |
| DEPE              | 1,2-Bis(diethylphosphino)ethane  |
| Diglyme           | Diethylene glycol dimethyl ether   |
| (+)-DIOP          | <i>O</i> -Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane                      |
| DIPEA             | <i>N,N</i> -Diisopropylethylamine  |
| DMA               | <i>N,N</i> -Dimethylacetamide  |
| DMB               | 4,4-Dimethoxy-2-butanone   |

|              |   |
|--------------|---|
| DME          | 1,2-Dimethoxyethane                                     |
| DMF          | <i>N,N</i> -Dimethylformamide                           |
| DMPU         | 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone          |
| DMSO         | Dimethylsulfoxide                                       |
| DPE-Phos     | Bis-[2-(diphenylphosphino)phenyl]ether                  |
| DPPB         | 1,4-Bis(diphenylphosphino)butane                        |
| DPPE         | 1,2-Bis(diphenylphosphino)ethane                        |
| DPPF         | 1,1'-Bis(diphenylphosphino)ferrocene                    |
| DPPP         | 1,3-Bis(diphenylphosphino)propane                       |
| DTBPY        | 4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine             |
| DVB          | Divinylbenzene  |
| equiv        | Equivalents   |
| Et           | Ethyl   |
| g            | Grams   |
| h            | Hours   |
| HFIP         | Hexafluoro-2-propanol                                   |
| Hz           | Hertz   |
| ICP-AES      | Inductively coupled plasma atomic emission spectroscopy |
| ICP-MS       | Inductively coupled plasma mass spectrometry            |
| <i>i</i> -Pr | Isopropyl   |
| KHMDS        | Potassium bis(trimethylsilyl)amide                      |
| KPS          | Potassium peroxydisulfate                               |
| L            | Litres  |
| LC-MS        | Liquid chromatography mass spectrometry                 |
| M            | Mega  |
| m            | Milli   |
| Me           | Methyl  |
| Mes          | Mesityl   |

|                |   |
|----------------|---|
| MIDA           | <i>N</i> -Methyliminodiacetic acid  |
| mol            | moles   |
| MTBE           | Methyl- <i>tert</i> -butyl ether  |
| NASS           | Sodium styrene sulfonate  |
| NHC            | <i>N</i> -Heterocyclic carbene  |
| NMP            | <i>N</i> -Methylpyrrolidone   |
| NMR            | Nuclear magnetic resonance spectroscopy   |
| PCA            | Principle component analysis  |
| PEPPSI-IPr     | [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride |
| PEPPSI-SIPr    | (1,3-Diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride                |
| Ph             | Phenyl  |
| Pin            | Pinacol   |
| Piv            | Pivaloyl  |
| PVP            | Polyvinylpyrrolidone  |
| PVPy           | Polyvinylpyridine   |
| Q-Phos         | 1,2,3,4,5-Pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene                         |
| <i>R</i> -PPTL | <i>N</i> -Phthaloyl-( <i>R</i> )- <i>tert</i> -leucinate                                    |
| rt             | Room temperature  |
| TBAB           | Tetrabutylammonium bromide  |
| TBAF           | Tetrabutylammonium fluoride   |
| TBHP           | Tertiarybutylhydroperoxide  |
| TBP            | Tertiarybutylperoxide   |
| <i>t</i> -Bu   | Tertiarybutyl   |
| Tf             | Triflate  |
| TFA            | Trifluoroacetic acid  |
| TFAA           | Trifluoroacetic anhydride   |

|         |   |
|---------|---|
| TMEDA   | <i>N,N,N',N'</i> -Tetramethylethylenediamine                |
| TMS     | Trimethylsilyl  |
| TPPTS   | Triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt |
| Triphos | 1,1,1-Tris(diphenylphosphinomethyl)ethane                   |
| Ts      | Tosyl   |
| X-Phos  | 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl       |

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In particular, I acknowledge the use of LC-MS data collected by Dr Patricia Marce-Villa, which is presented as part of the results and discussion in Chapter 2, Figures 2.1 and 2.2, pages 45-46.

We can change by doing different things, but also by doing the same things differently. We can do the same things differently by using different materials, methods or tools, within the same broad understanding of what we are doing and why – but also, by coming to understand our purposes and rationale differently. Such a changed understanding can liberate us, in turn, to a new imagining of possibilities, of the prospects and opportunities really open to us.

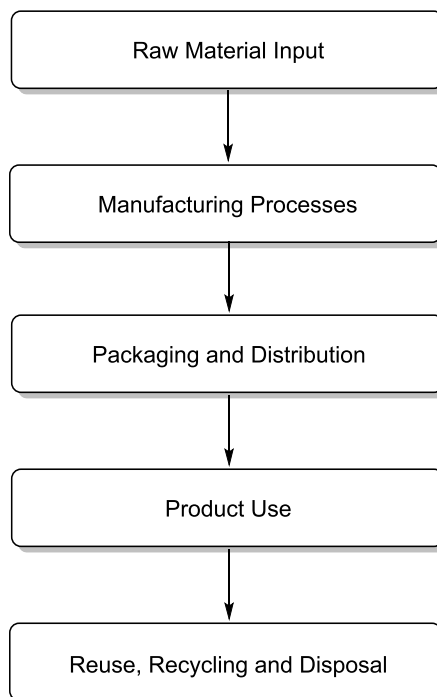
- *John Foster, The Sustainability Mirage*

# 1. Introduction

## 1.1 Green Chemistry and Sustainability

Green Chemistry is concerned with the development and application of environmentally benign chemical products and processes which minimise the negative impacts that chemistry and in particular the chemical industry has on both human health and the environment.<sup>1</sup> It is seen as a philosophy more than a discipline and as such its activities encompass all branches of chemistry; organic, inorganic, physical, analytical and computational to achieve its objectives.

Green chemistry is often cited as having a 'cradle to grave' (Figure 1.1) approach to the way it looks at a process; considering the raw material acquisition, all the way through the lifecycle, to product disposal. This includes all inputs in terms of materials and energy, all substances generated during the process such as useful products, intermediates or wastes, the use of that product and then the subsequent disposal of all the materials involved.



**Figure 1.1** Cradle to grave lifecycle



Looking at a process comprehensively in this way allows the areas with the biggest impacts to be identified, assessed and improved.<sup>2</sup> It also allows individuals involved in the process to see the whole picture not just their own part in it, so that problems can be anticipated in advance and they are not just passed on down the line for someone else to deal with later on in the process.

#### **1.1.1 The 12 Principles of Green Chemistry**

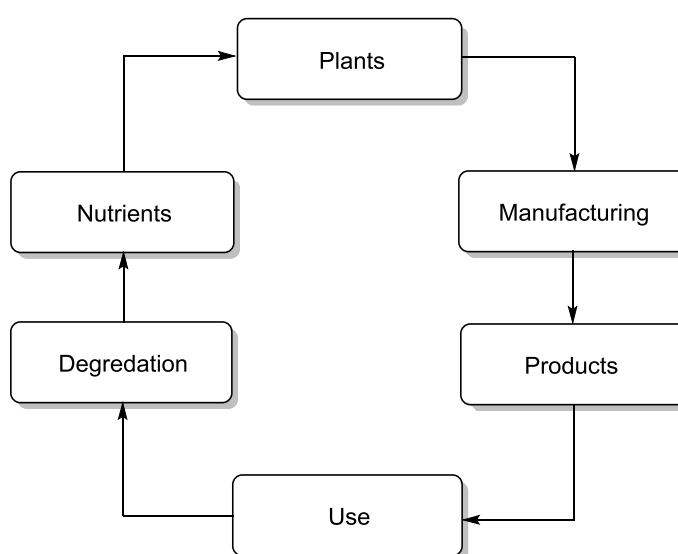
In 1998 Paul Anastas and John Warner published their seminal book; *Green Chemistry: Theory and Practice*,<sup>3</sup> in which they set out the 12 Principles of Green Chemistry that act as a code of best practice for designing and implementing new chemical processes, with the aim of minimising their environmental impact. They cover all aspects of chemistry from raw materials, solvents and catalysts to production, waste and reaction monitoring.

1. *Waste prevention*
2. *Atom economy*
3. *Minimise the use hazardous chemicals*
4. *Design safer chemical products*
5. *Minimise solvents and auxiliaries*
6. *Energy efficiency*
7. *Renewable feedstocks*
8. *Reduce derivatisations*
9. *Catalysis*
10. *Product degradation*
11. *Real-time analysis*
12. *Inherently safer chemical processes*

#### **1.1.2 Sustainability**

Although sustainability is one of the key long term aims of green chemistry and they undoubtedly share many of the same goals, the two terms are not synonymous.<sup>4</sup> Much like green chemistry, sustainability warrants the adoption of a lifecycle approach to assessing a problem, but the difference lies in how far the lifecycle assessment goes.

Sustainability can be considered to have a 'cradle to cradle' (Figure 1.2) assessment model which, in addition to incorporating all of the inputs and outputs of the green chemistry model, also considers how quickly the outputs break down to be assimilated into the environment and how long it takes for the raw materials to be renewed, thus completing the cycle.<sup>5</sup> It can be said then that the move towards a truly sustainable society requires both the widespread adoption of green chemistry ideas and practices and the sourcing of raw materials from truly renewable feedstocks, for the production of commodity chemicals and products.<sup>6</sup>



**Figure 1.2** Cradle to cradle lifecycle

### **1.1.3 E Factors and Pharmaceuticals**

An E Factor is a measure of how much waste is produced in a process, relative to the amount of useful product(s) obtained. The concept was developed by Roger Sheldon<sup>7</sup> in 1992 as a way of quantifying how wasteful a process is, by comparing the ratio of waste to product produced. It was the first of many green chemistry metrics to be developed,<sup>8</sup> but still remains one of the simplest and most widely applicable. The E Factor can most readily be defined as kilograms of raw materials in, minus kilograms of desired product, divided by kilograms of product out (Equation 1.1).<sup>3</sup>

$$E \text{ Factor} = \frac{\text{Raw Material IN (kg)} - \text{Product OUT (kg)}}{\text{Product OUT (kg)}}$$

**Equation 1.1** The E Factor

E Factors can be made to be as simple or comprehensive as required and by making assumptions about things like solvent recycling or use of auxiliaries. In general it can take into account any inputs the user wishes to include, even energy use by including estimations of carbon dioxide and other gaseous emissions into waste calculations. Although there is usually one exception to this; water is often not included in the calculations because it leads to very high E Factors and can make it hard for meaningful comparisons to be made between two different processes.<sup>9</sup>

Pharmaceutical manufacture is at the high value, low volume end of the chemical market, and as such it is often thought of as having a relatively low environmental impact and producing a small volume of waste, in comparison to the petrochemicals industry. But this is not strictly true. If a comparison is made between the E Factors of these industries, the opposite can be seen to be the case. Table 1.1 shows the E Factor and amount of waste produced, in tonnes, of different sectors within the chemical industry.<sup>9</sup>

**Table 1.1** E factors of different sections of the chemical industry

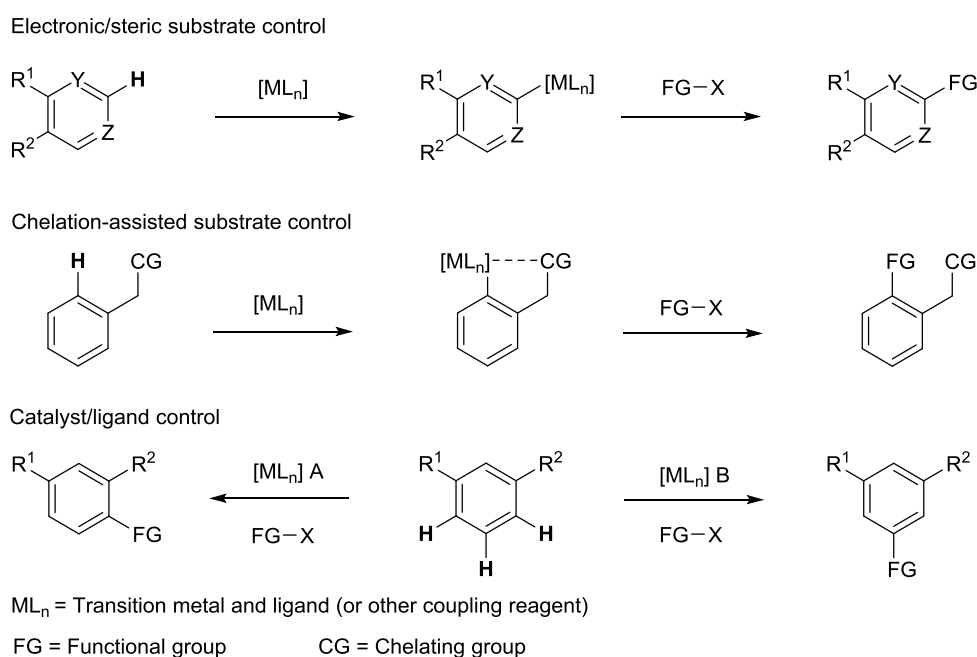
| Entry | Industry Sector | Product Tonnage | E Factor  |
|-------|-----------------|-----------------|-----------|
| 1     | Oil Refining    | $10^6 - 10^8$   | <0.1      |
| 2     | Bulk Chemicals  | $10^4 - 10^6$   | <1 - 5    |
| 3     | Fine Chemicals  | $10^2 - 10^4$   | 5 - 50    |
| 4     | Pharmaceuticals | $10 - 10^3$     | 25 - >100 |

In terms of the amount of waste produced per kg of useful product, the pharmaceuticals sector is the most wasteful of the whole of the chemicals industry, with E Factors almost 1000 times bigger than the oil refining sector. This is mainly due to the much greater efficiencies in processing developed by the oil industry over the last century. Petrochemical processing is routinely conducted on a continuous-flow basis and utilises

heterogeneous catalysts, most commonly zeolites,<sup>10</sup> to affect the cracking process, which can be recycled and reused many times, often only being replaced every 1-2 years.<sup>11</sup> It is this efficiency that is now driving research and development in the use of new, more efficient catalytic processes in conjunction with continuous-flow systems for the pharmaceutical and fine chemical sectors.<sup>12, 13</sup>

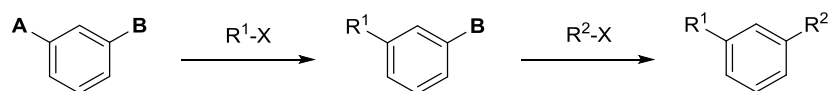
## 1.2 Catalytic C-H Functionalisation

The development of regioselective C-H functionalisation processes has received a lot of interest in recent years, in an effort to develop new and more efficient synthetic methodologies for the production of complex molecules and fine chemicals. Moreover the ability to functionalise multiple C-H bonds in an iterative fashion serves to enhance the efficacy of this methodology further, with the potential to provide access to highly functionalised molecular architectures using shorter synthetic routes than via conventional chemical transformations. Combining direct C-H functionalisations with other processes can also lead to new and improved synthetic methodologies and chemical compounds.

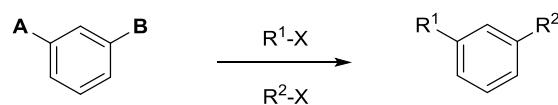


**Scheme 1.1** Controlling regioselectivity in C-H functionalisation processes

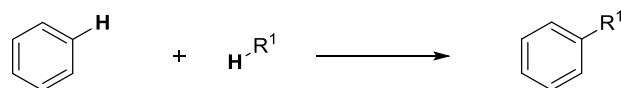
Sequential functionalisation (This review)



Tandem functionalisation



Cross-dehydrogenative coupling (CDC)



**Scheme 1.2** Sequential, tandem and cross-dehydrogenative coupling

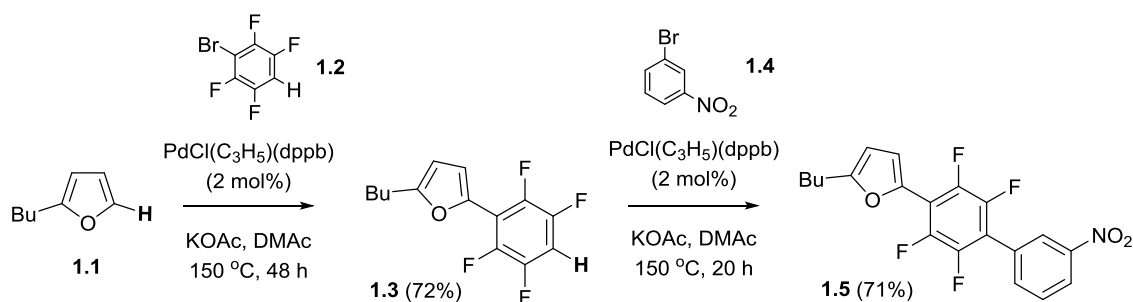
Common methods for controlling the selectivity of C-H functionalisation processes in substrates that contain multiple C-H bonds, can be categorised as one of three approaches.<sup>14</sup> The first relies upon the inherent electronic or steric nature of the substrates. This is most prevalent in electron rich heterocycles where the C-H bond at C2, adjacent to the heteroatom, is far more reactive than the others and hence shows selectivity towards activation. The second involves the use of a chelating (or directing) group, often containing a heteroatom, that coordinates to the transition metal and facilitates functionalisation of a neighbouring C-H bond.<sup>15</sup> This serves to distinguish between C-H bonds in seemingly identical steric and electronic environments, thus providing a high degree of control over the reaction selectivity. The third and perhaps most powerful method is via catalyst/ligand control. By changing the ligand on the transition metal its reactivity can be switched to favour activation at different sites. Certain catalysts can also overcome inherent bias in the substrates and provide complementary reactivity to the first two substrate controlled methods (Scheme 1.1).

This review will highlight selected examples of sequential reaction protocols that involve at least one C-H functionalisation as the key synthetic step. In the context of the review sequential processes will be defined as the functionalisation of two or more bonds on the same substrate with each one occurring as the result of separate consecutive unit operations, either in isolated reaction steps or as a one pot process. Tandem processes, which involve the functionalisation of two or more bonds on the same substrate, within the confines of a single unit operation will not be covered.<sup>16</sup> A detailed discussion of

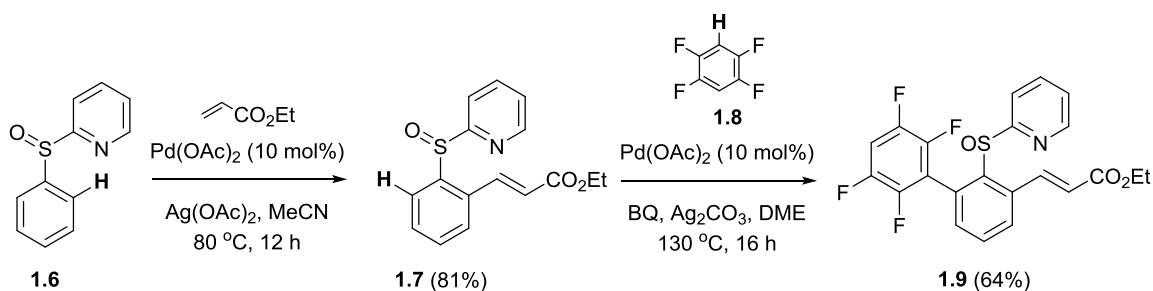
cross-dehydrogenative coupling (CDC) reactions that couple two C-H bonds on different substrates together to form a new C-C bond is outside the scope of this review,<sup>17</sup> however some of the sequential examples discussed will involve CDC reactions (Scheme 1.2). The first part of the review deals with sequential processes involving direct selective functionalisation of multiple C-H bonds. Focus will then move on to how C-H functionalisations can be used in conjunction with other synthetic methods, including cross-couplings and finally examples of directing group modifications that can be used to achieve interesting molecular motifs will be explored.

### 1.2.1 Sequential C-H functionalisations

An example of sequential C-H bond functionalisations with aryl halides was described by Dixneuf, exploiting the difference in reactivity between C-H bonds on heteroarenes and polyfluorinated benzenes using  $\text{Pd}(\text{OAc})_2$  as the catalyst for both steps.<sup>18</sup> First was the arylation of a 5-membered heteroarene **1.1** at C5 using bromotetrafluorobenzene **1.2** which was shown to give **1.3** in good yield with no homocoupled product observed, highlighting the different reactivities of these C-H bonds. These coupled products could



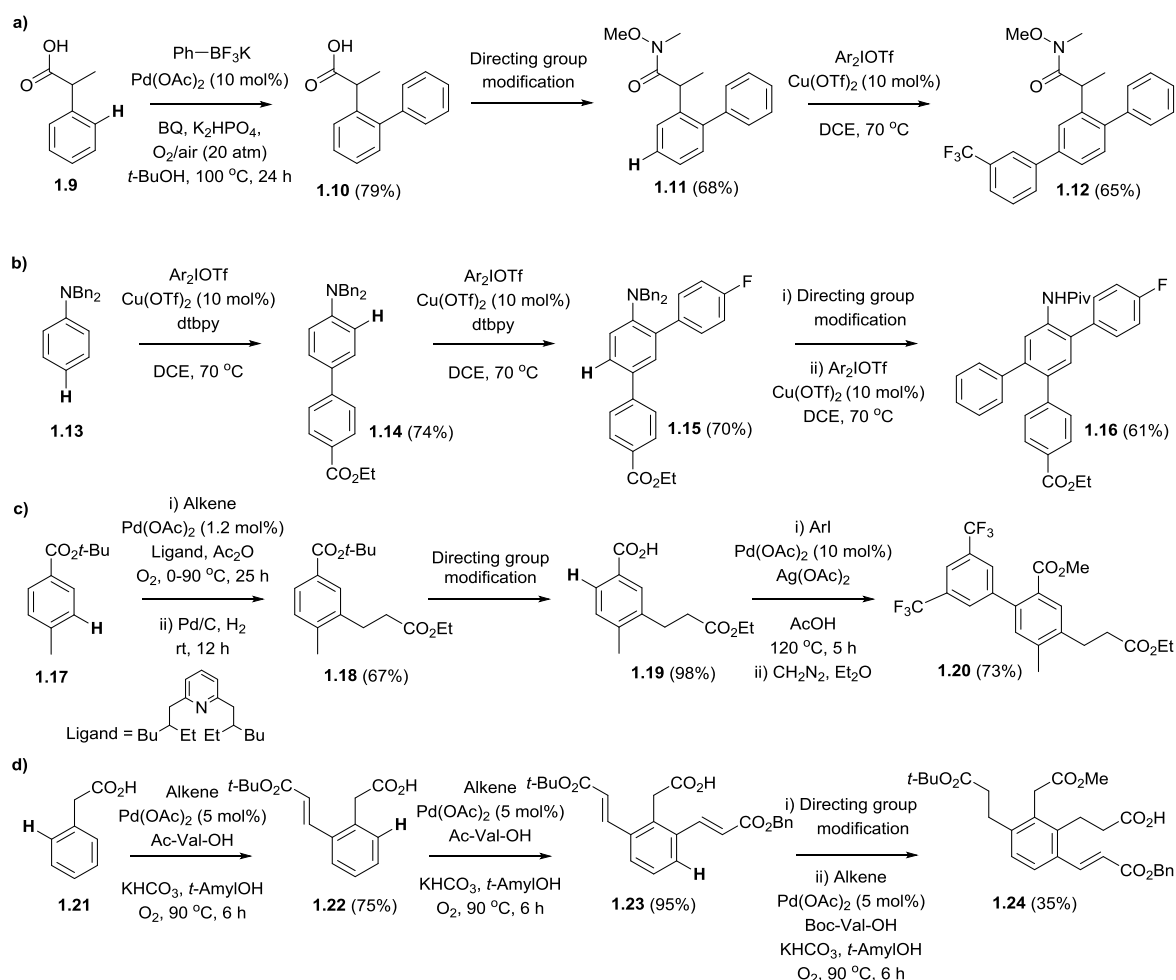
**Scheme 1.3** C-H functionalisations controlled by polyfluorinated arenes



**Scheme 1.4** Chelation-assisted *ortho, ortho* functionalisation

then be further functionalised by arylation at C6 on the tetrafluoroarene ring to give a range of polyfluorinated biphenyls such as **1.5** (Scheme 1.3). Site selectivity in the second step was controlled by use of the fluorine substituents which served to simultaneously activate the required C-H bond, while blocking the other sites on the arene toward functionalisation.

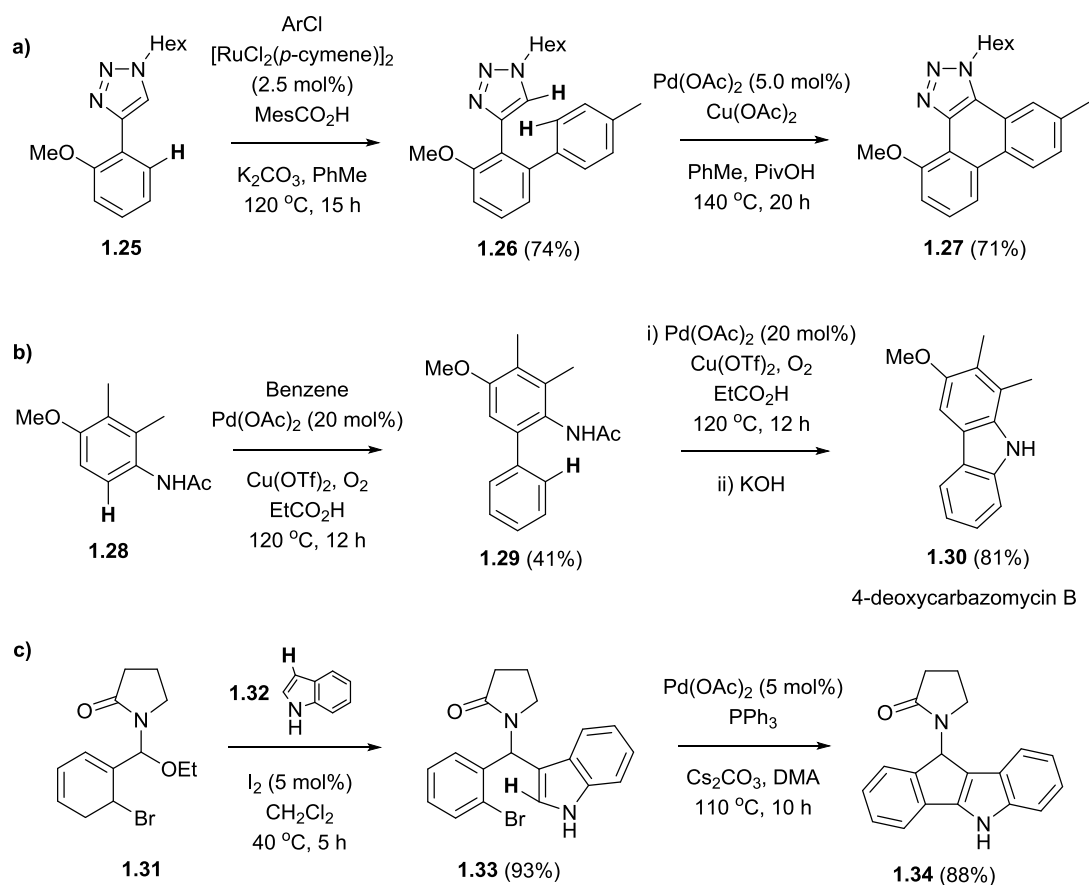
Another strategy to control regioselectivity in the functionalisation of arenes is to use a directing group. Zhang and co-workers reported the sequential *ortho*, *ortho* functionalisation of monosubstituted arenes using a sulfinylpyridine substituent as a directing group.<sup>19</sup> Alkenylation was achieved using a Pd(OAc)<sub>2</sub> catalysed oxidative coupling, followed by a Pd(OAc)<sub>2</sub> catalysed arylation, with polyfluorinated benzene derivative **1.8** (Scheme 1.4). Both steps being examples of CDC reactions in which functionalisation of C-H bonds occur on both coupling partners. A similar strategy using an *ortho*, *meta* sequence has been employed by Gaunt to functionalise  $\alpha$ -arylacetamides.<sup>20</sup> A Cu(OTf)<sub>2</sub> catalysed *meta* arylation methodology utilising a non-chelating remote directing group was first developed, making use of diaryliodonium triflates as the coupling partners. This was then utilised in a sequential protocol, preceded by a Pd-catalysed arylation of the *ortho* position. The selectivity of each step is governed by the electronic nature of the arene, which in turn is determined by the directing group. Thus it was necessary to perform a modification from carboxylic acid **1.10** to the corresponding amide **1.11** in between C-H functionalisations (Scheme 1.5a). Moreover the same methodology was then extended to encompass an additional *para* functionalisation, with a *para*, *ortho*, *meta* sequence being devised for the functionalisation of anilines.<sup>21</sup> Once again this required a small modification of the remote directing substituent from *N,N*-dibenzylaniline **1.14** to *N*-pivaloylaniline **1.15** between *ortho* and *meta* functionalisation, but this time all three steps were catalysed by Cu(OTf)<sub>2</sub> (Scheme 1.5b). Yu showcased an example of a *meta*, *ortho* sequence utilising both chelating and non-chelating directing groups.<sup>22</sup> The initial *meta* alkenylation of *t*-butylester **1.17**, catalysed by Pd(OAc)<sub>2</sub>, made use of a dialkylpyridine ligand to give **1.18** in good yield. The ester was then modified to carboxylic acid **1.19** and used as a chelating group for the subsequent *ortho* arylation step, which was also Pd-catalysed (Scheme 1.5c). The same group then went on to implement sequential alkenylations for the construction of sterically congested arenes, again directed by carboxylic acids.<sup>23</sup> The Pd-



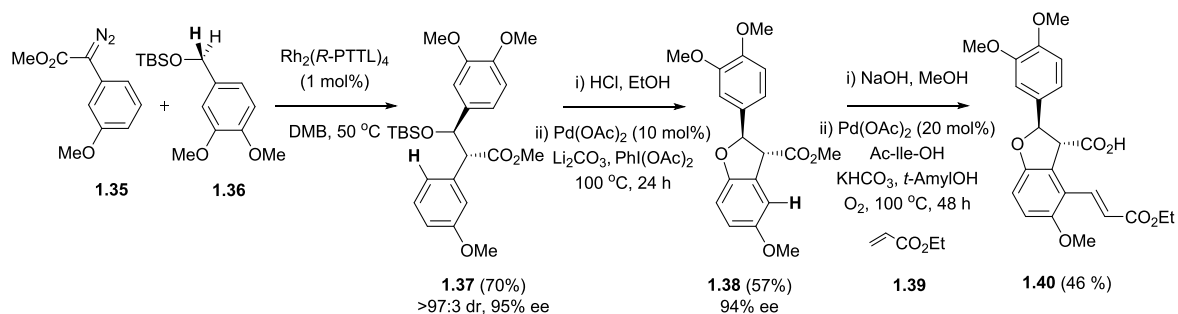
**Scheme 1.5** C-H functionalisation sequences enabled by modification of the directing groups

catalysed strategy consisted of two distinct *ortho* alkenylations followed by conversion of the carboxylic acid **1.23** to a methyl ester and hydrogenation of the benzyl ester, to facilitate a third alkenylation *ortho* to the newly uncovered carboxylic acid to afford tetra-substituted benzene derivative **1.24** (Scheme 1.5d). In addition to the functionalisation of arenes, sequential C-H activation processes have also been used to access polycyclic and heterocyclic motifs. Ackermann illustrated an efficient route to annulated phenantrenes using a Ru-catalysed *ortho* arylation of 4-aryl-1,2,3-triazoles **1.25**, followed by a Pd-catalysed cyclodehydrogenative cyclisation (Scheme 1.6a).<sup>24</sup> This was shown to be applicable to arenes bearing a variety of functional groups, including ketones and esters. The construction of substituted carbazoles, including 4-deoxycarbazomycin B **1.30** has been achieved through cross-dehydrogenative coupling of two arenes directed by an acetate group, utilising Pd(OAc)<sub>2</sub> and Cu(OTf)<sub>2</sub> as an oxidative co-catalyst, again followed by an intramolecular C-N coupling.<sup>25</sup> The acetate directing group could then be removed



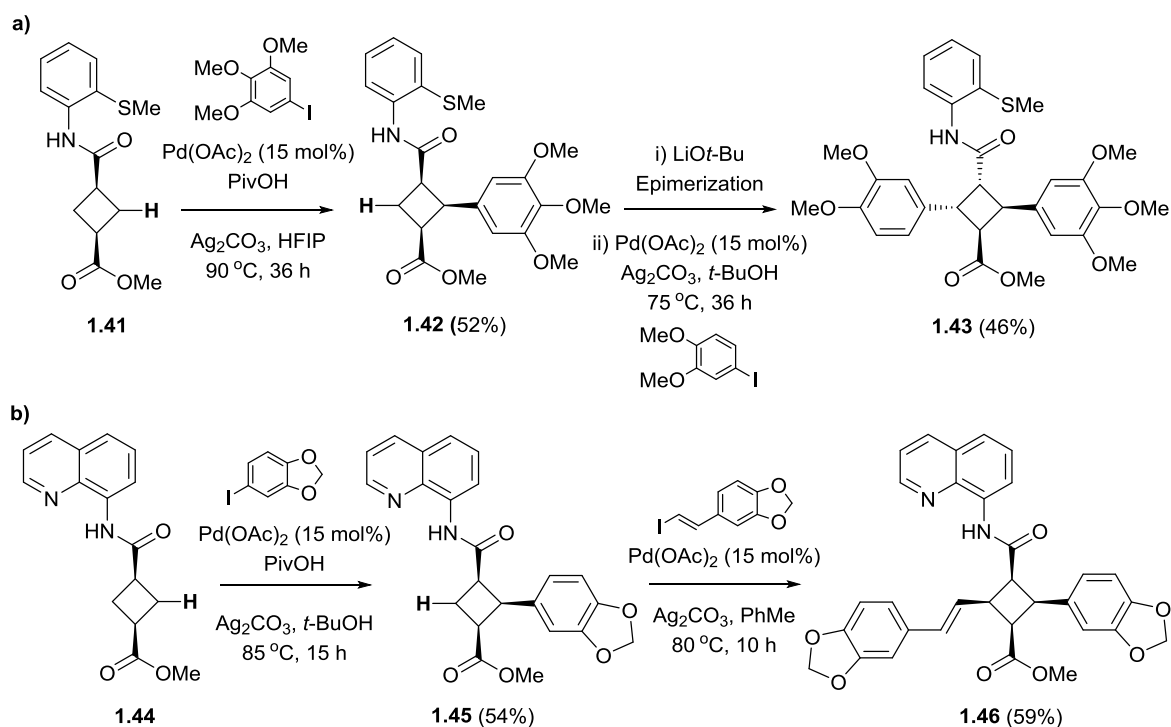


**Scheme 1.6** Heterocycle synthesis via sequential C-H functionalisations



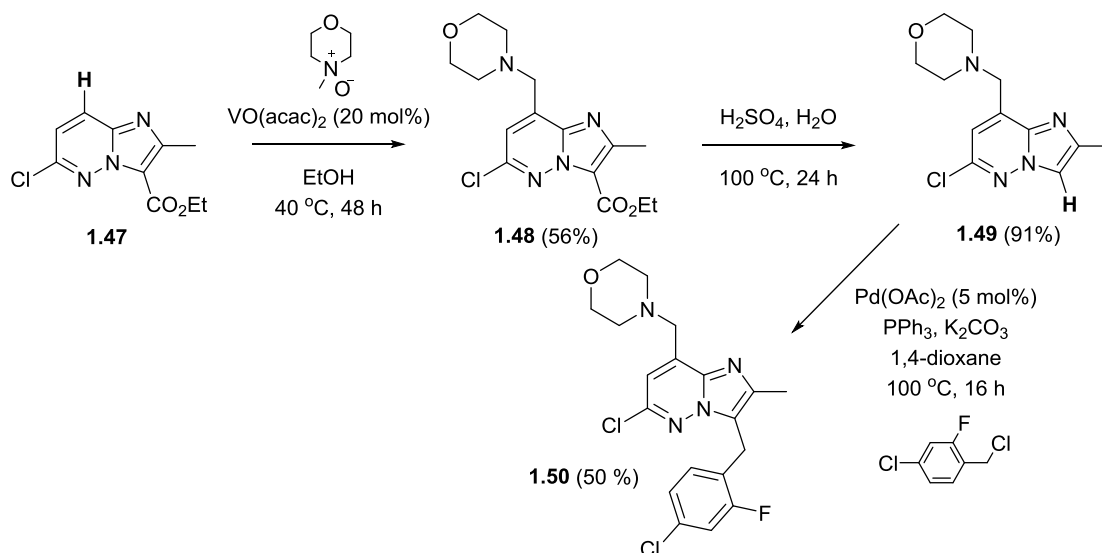
**Scheme 1.7** Enantioselective synthesis of highly substituted 2,3-dihydrobenzofurans

to reveal the unprotected carbazole derivative (Scheme 1.6b). Notably this was achieved solely through the coupling C-H and N-H bonds without the use of any halides or organometallic reagents. Indeno[1,2-*b*]-indole derivatives have been synthesised from indoles **1.32** via sequential functionalisations at C3 and C2 respectively.<sup>26</sup> A mild  $\text{I}_2$  catalysed alkylation at C3 and a Pd-catalysed intramolecular C-N coupling at C2 yielded



**Scheme 1.8** Synthesis of complex natural products via sequential functionalisation of a cyclobutane core

several Indeno[1,2-*b*]-indole derivatives **1.34** which may have potential biological activity (Scheme 1.6c). An elegant enantioselective synthesis of 2,3-Dihydrobenzofurans has been outlined by Yu and Davies.<sup>27</sup> An initial C-H functionalisation of benzyl ether **1.36** was shown to proceed in good yield, with excellent enantioselectivity (95% ee) and diastereoselectivity (>97:3 dr) being imparted by the chiral  $\text{Rh}_2(R\text{-PTTL})_4$  catalyst (Scheme 1.7). A subsequent deprotection of the alcohol paved the way for an intramolecular Pd-catalysed cyclisation to dihydrobenzofuran **1.38**. It was noted that this step proceeded with good regioselectivity, 13:1 in favour of the C-H bond *para* to the methoxy substituent and no epimerisation or racemisation was observed. To take things further a third functionalisation was devised, which required hydrolysis of the ester to a carboxylic acid to provide a directing group for a Heck-type CDC with alkene **1.39** affording highly functionalised benzofuranylacrylate **1.40**, similar in structure to lithospermic acid, a complex natural product. Baran et al. have exploited the sequential functionalisation of  $\text{sp}^3$  C-H bonds in the synthesis of natural products (Scheme 1.8). Piperarborenine B and Piperarborenine D were both synthesised via divergent pathways from intermediate **1.42** using the first reported examples of the direct C-H arylation of cyclobutane.<sup>28</sup> From

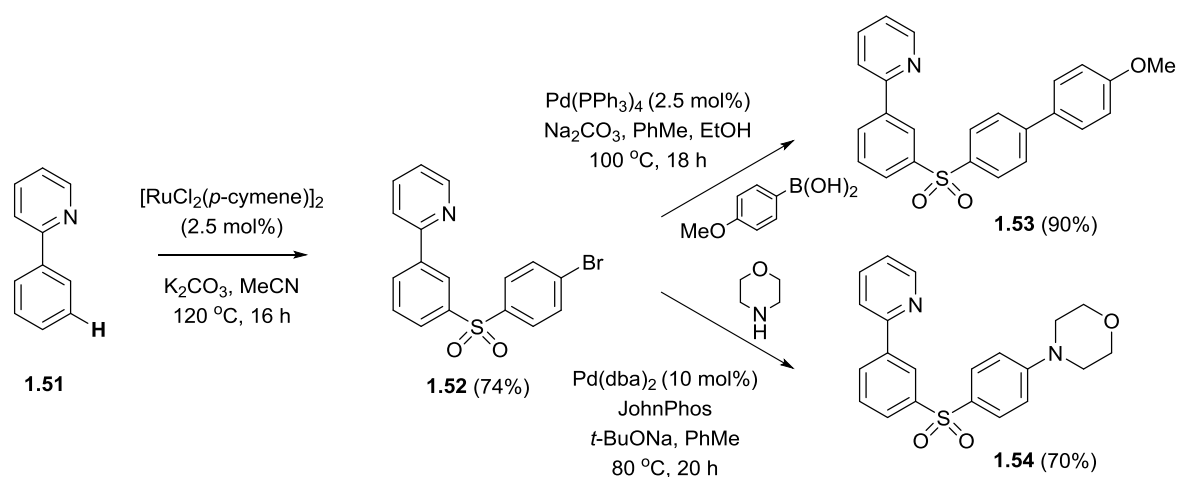


**Scheme 1.9** Alternative route to an intermediate in the production of a promising JAK2 inhibitor

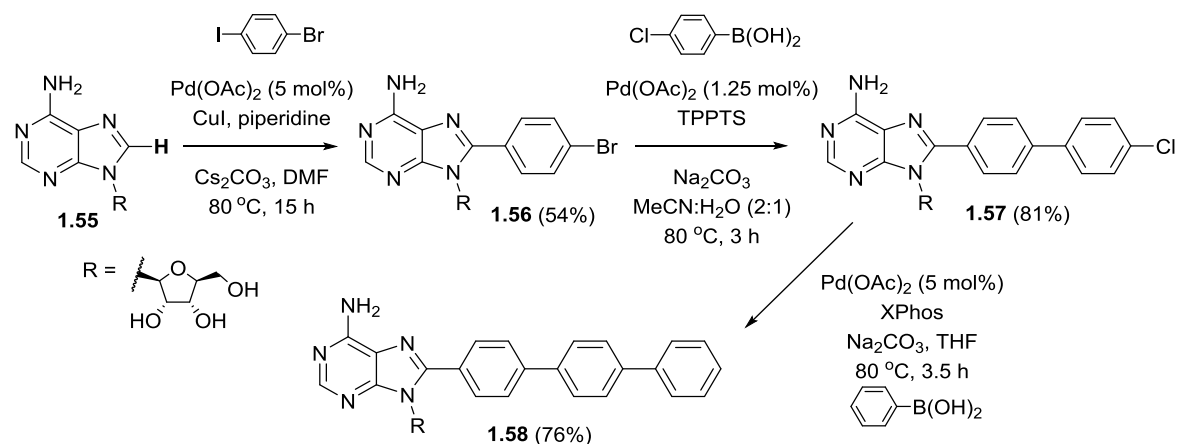
intermediate **1.41** a  $\text{Pd}(\text{OAc})_2$  catalysed arylation with an aryl iodide afforded key intermediate **1.42**. Formation of the diarylated product at this stage was avoided by the addition of hexafluoroisopropanol (HFIP) and pivalic acid. From there the synthesis diverged with opposing epimerizations, followed by a second Pd-catalysed arylation with the stereochemistry of each arylation being determined by the directing group. Subsequent modification of the directing group and methyl ester furnished both natural products (Scheme 1.8a). This work was then extended to the total synthesis of pipericyclobutanamide A, from intermediate **1.46**, using an amidoquinoline directing group and  $\text{Pd}(\text{OAc})_2$  to facilitate an arylation, alkenylation sequence on a cyclobutane core (Scheme 1.8b).<sup>29</sup> Campbell and co-workers from Eli Lilly have developed a sequential process for the production of **1.50**, an intermediate in the synthesis of a promising JAK2 inhibitor.<sup>30</sup> The existing synthetic route suffered from long lead times and problems with waste incineration, which led to a re-evaluation of the process and investigation of possible alternatives. A  $\text{VO}(\text{acac})_2$  catalysed CDC between the  $\text{sp}^3$  C-H bond on *N*-methylmorpholine oxide (NMO) and the  $\text{sp}^2$  C-H bond at C8 on **1.47** furnished the benzylic morpholine intermediate **1.48** in good yield. After a decarboxylation to uncover the free C-H at C3, a Pd-catalysed benzylation gave the required intermediate **1.50** (Scheme 1.9). The new route was one step shorter than that previously described and with considerably less issues with waste disposal, although it was noted that, with the overall yield being significantly lower (16% vs. the previous 35%), the overall efficiency of the process was not as competitive as first hoped.

### 1.2.2 Sequential C-H functionalisation/cross-coupling

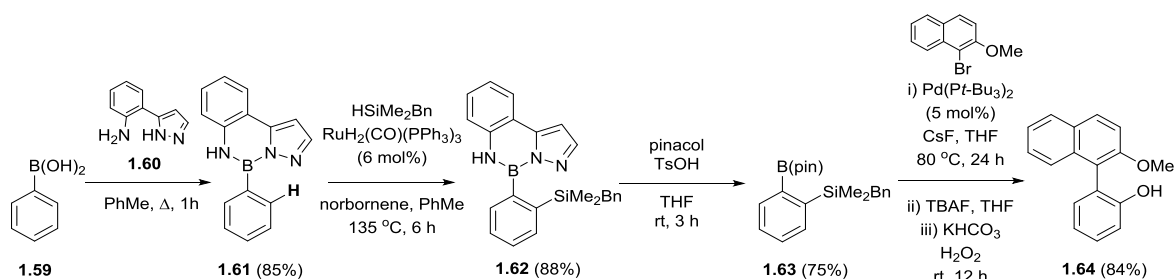
Although not perhaps as efficient as sequential C-H functionalisations, processes involving conventional cross-couplings can also prove useful in synthesis. Frost described a sequential process consisting of the Ru-catalysed *meta*-selective sulfonation of 2-phenylpyridine **1.51** with *p*-bromosulfonyl chloride and subsequent cross-coupling under Suzuki **1.53** and Buchwald-Hartwig **1.54** conditions, to provide access to extended polyaromatic compounds in just two steps (Scheme 1.10).<sup>31</sup> Taking the concept further, Fairlamb and Baumann reported a sequential methodology comprising the direct C-H arylation of 2'-deoxyadenosine derivatives **1.55** and two consecutive Suzuki cross-couplings.<sup>32</sup> The Pd(OAc)<sub>2</sub> catalysed arylation with aryl iodides proved entirely selective



**Scheme 1.10** Sequential *meta* functionalisation followed by divergent Suzuki cross-couplings

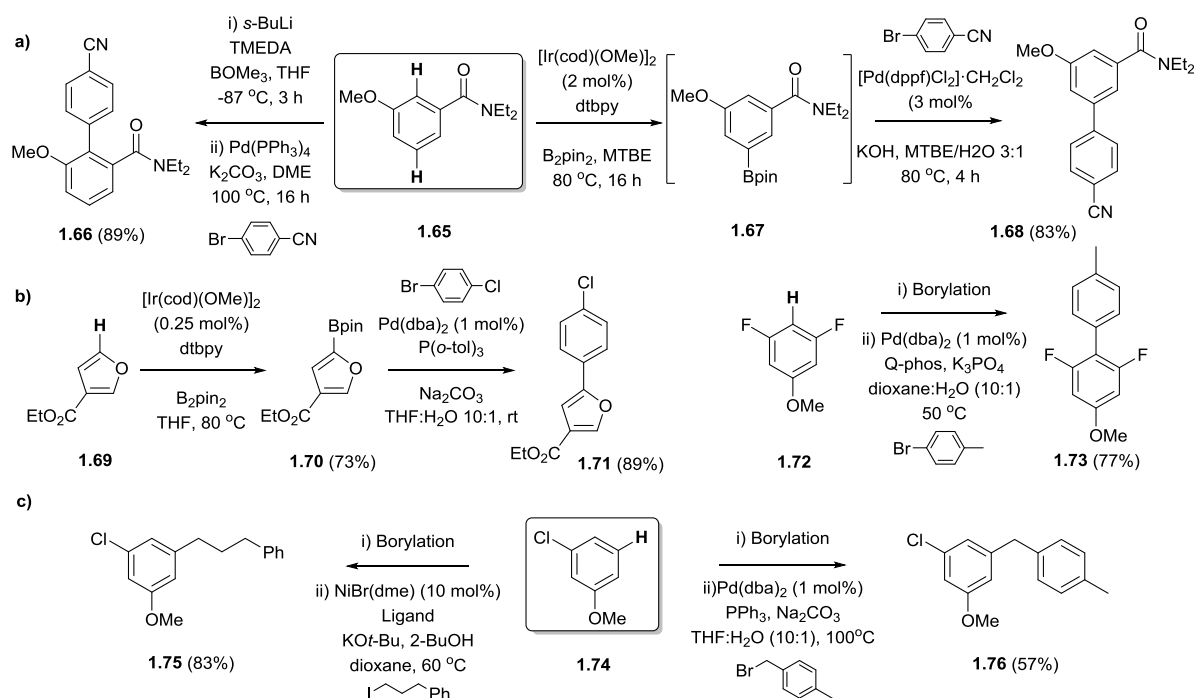


**Scheme 1.11** Sequential arylation followed by two consecutive Suzuki cross-couplings

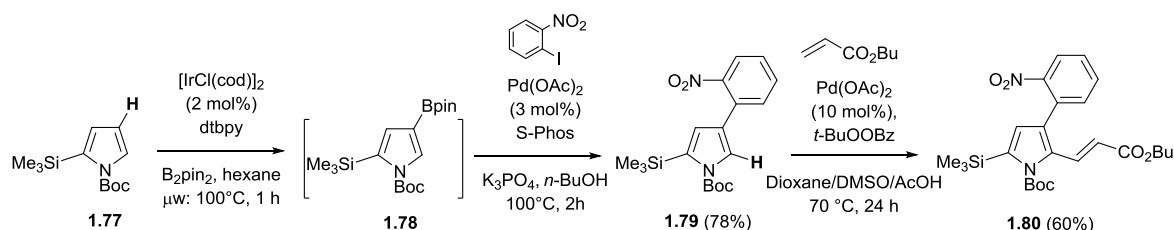


**Scheme 1.12** Sequential *ortho* functionalisation and cross-coupling of a removable protecting group for boronic acids

for coupling at C8, while exploiting the difference in reactivity between aryl bromides and aryl chlorides gave excellent yields in both Suzuki couplings, each utilising a different ligand to account for the reactivity difference (Scheme 1.11). The extended polyaromatic structures **1.58** were found to have potential as fluorescent probes. Ihara and Sugimoto pioneered the use of a detachable directing group for arylboronic acids that could facilitate direct functionalisation of the aryl ring before being removed to allow cross-coupling as pinacol esters.<sup>33</sup> It was found that 2-pyrazol-5-ylaniline (pza) **1.60** could be easily attached to a range of boronic acids and undergo  $\text{RuH}_2\text{CO}(\text{PPh}_3)_3$  catalysed silylation in excellent yield (Scheme 1.12). After conversion to the pinacol ester **1.63**, Suzuki coupling afforded access to *ortho* substituted biaryl motifs. As an extension to the sequence, the silyl group was converted to a hydroxyl moiety via Tamao-Fleming oxidation to afford naphthyl-substituted phenol **1.64**. Another valuable approach to combining C-H functionalisation and cross-coupling entails a regioselective borylation and subsequent Suzuki coupling methodology, which can be applied to the synthesis of highly substituted biphenyls and heteroaromatics.<sup>34</sup> Using *O*-carbamate and amide functionalities, known to be good directing groups for directed *ortho* metallation (DoM) reactions, opposing reaction sequences were devised which gave complementary regioselectivities (Scheme 1.13a). The first sequence of a DoM using *s*-BuLi quenched with  $\text{B}(\text{OMe})_3$ , followed by Suzuki coupling gave the *ortho*-arylated products **1.66**. While the second sequence entailed an Ir-catalysed borylation to give **1.67** followed by Suzuki coupling which afforded the *meta*-arylated products **1.68**. These two complementary pathways provide an example of how regioselective C-H functionalisation methodologies can be powerful tools for divergent chemical synthesis. A similar protocol was developed by Robbins and Hartwig for the sequential borylation and Suzuki coupling of challenging

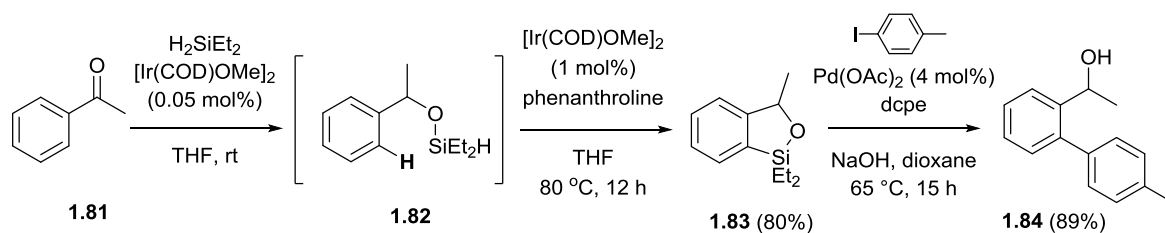


**Scheme 1.13** Applications of C-H borylation and subsequent cross-coupling at the same site



**Scheme 1.14** Highly substituted pyrroles via a C-H borylation/cross-coupling and alkenylation sequence

heteroaryl and polyfluorophenyl substrates.<sup>35</sup> Again using an iridium catalyst, borylation at C2 for the heterocycles and at the least sterically hindered site *ortho* to the fluorine substituents for the fluoroarenes, occurred in good yield. Subsequent Suzuki coupling also proceeded in high yield under mild reaction conditions (Scheme 1.13b). It was noted that this one-pot procedure gave higher yields of the cross-coupled product compared to the analogous reaction with the isolated pinacol boronates. A recent expansion of this methodology encompasses alkylation **1.75** and benzylation **1.76** of borylated intermediates, using Pd and Ni catalysts, with the same site-selectivities (Scheme 1.13c).<sup>36</sup> Gaunt and co-workers have taken this concept one step further by utilising a regioselective borylation/cross-coupling as part of a sequential C-H functionalisation

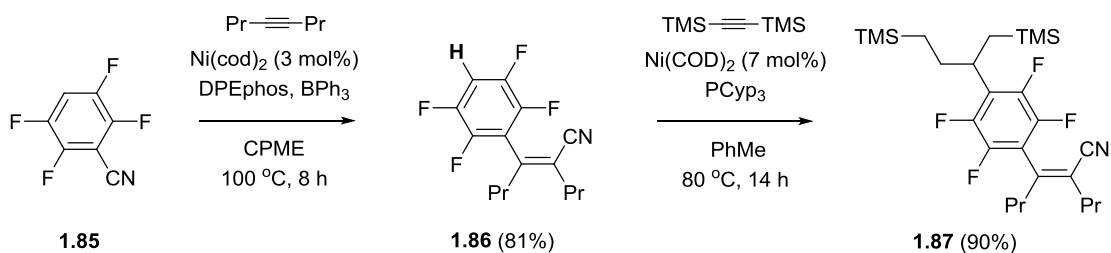


**Scheme 1.15** Sequential *ortho* silylation followed by Hiyama cross-coupling

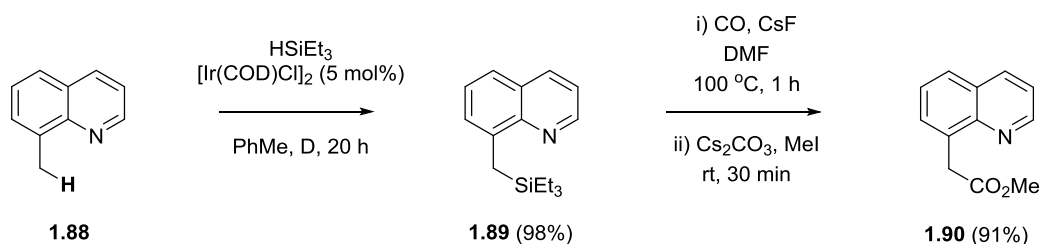
strategy for the synthesis of highly-substituted pyrroles.<sup>37</sup> The Ir-catalysed borylation at C3 afforded pinacol borane analogue **1.78** which was used in situ for a Suzuki coupling to give **1.79**. A further Pd-catalysed C-H alkenylation at C2 was then incorporated to yield trisubstituted pyrrole **1.80** (Scheme 1.14). In previous examples the authors have demonstrated a switch in selectivity for C-H alkenylation of pyrroles from C2 to C3 by careful choice of *N*-substituents<sup>38</sup> and a protocol for the sequential alkenylation of indoles and both C2 and C3.<sup>39</sup> In addition to Suzuki couplings, Simmons and Hartwig illustrated a sequential one-pot process based on the Hiyama coupling, with the generation of a silyl intermediate via C-H functionalisation.<sup>40</sup> Formation of the cyclised intermediate **1.81** proceeded via an Ir-catalysed intramolecular hydrosilylation of the corresponding aldehyde, ketone or benzyl alcohol. Hiyama coupling of **1.83** with aryl halides proceeded in good yield to give the *ortho*-arylated products **1.84** (Scheme 1.15). Subsequent C-O bond formation was also possible via a Tamao-Fleming oxidation of **1.83**.

### 1.2.3 Sequential C-H functionalisation/other transformation

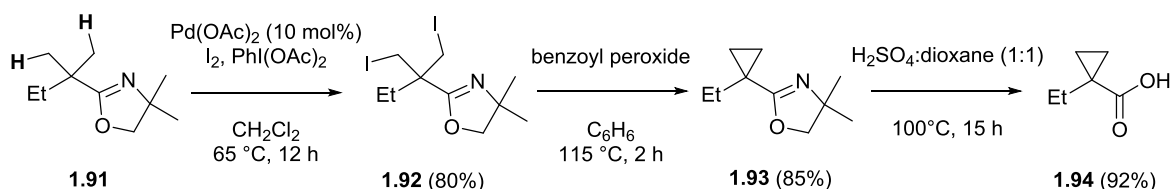
In addition to cross-couplings, several other transformations have been utilised as part of sequential methodologies. Another possible transformation of the *meta*-selective Ir-catalysed borylation methodology described by Hartwig is their subsequent conversion to halides including iodides,<sup>41</sup> as well as bromides and chlorides.<sup>42</sup> Hiyama et al. have achieved the sequential functionalisation of aromatic C-C and C-H bonds using alkynes.<sup>43</sup> Once again a polyfluorinated benzene was employed as the substrate, bearing both a cyano substituent and a free C-H bond (Scheme 1.16). The Ni(cod)<sub>2</sub> catalysed processes were used for both steps, the first being alkyne insertion into the C-CN bond to give alkene **1.86** and then another alkyne insertion into the C-H bond to give hexasubstituted



**Scheme 1.16** Sequential C-C/C-H bond functionalisation



**Scheme 1.17** Silylation/carboxylation of  $sp^3$  C-H bonds



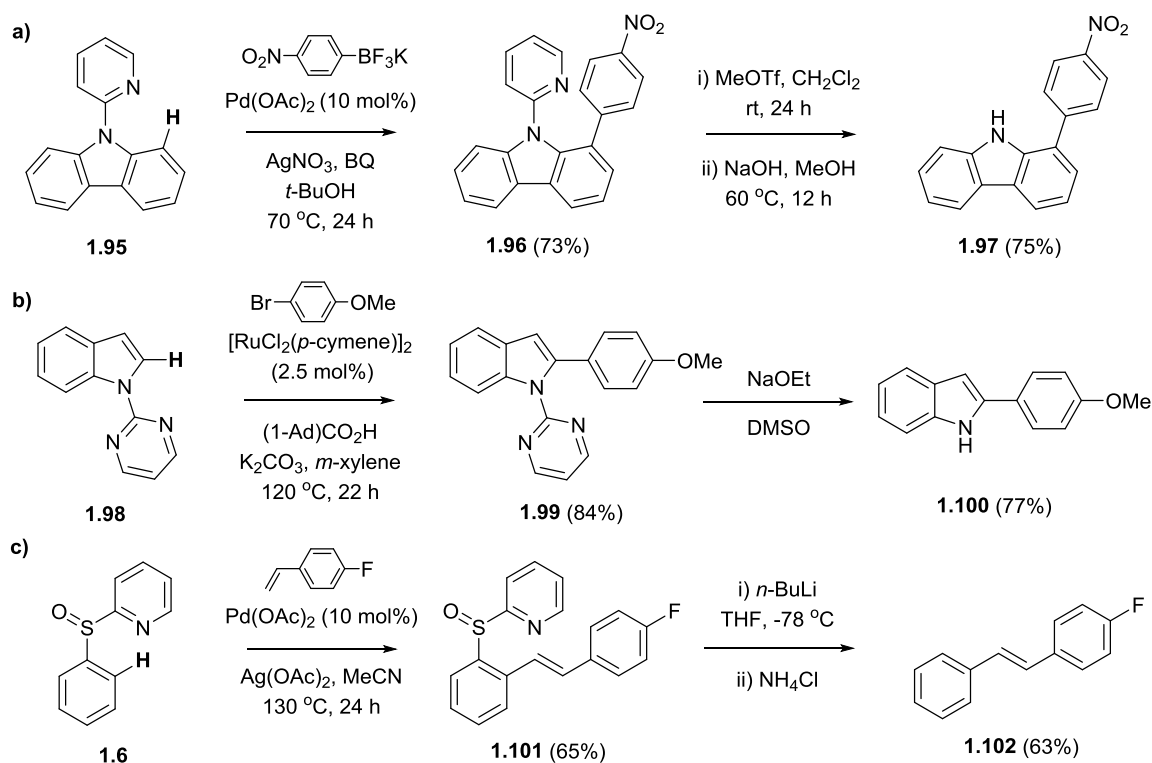
**Scheme 1.18** Synthesis of cyclopropane derivatives

arene **1.87**, in a one-pot process. Mita and co-workers designed a silylation protocol of  $sp^3$  C-H bonds followed by fluorine-mediated selective carboxylation of the C-Si bond, to yield the corresponding methyl ester.<sup>44</sup> Quinoline and *ortho*-methyl phenylpyridine derivatives were subjected to a silylation catalysed by either  $Ru(CO)_{12}$  or  $[Ir(cod)Cl]_2$  to give silylated products such as **1.89**. The benzylsilane moiety could then be converted to the methyl ester **1.90** using CO in the presence of CsF, followed by addition of methyl iodide (Scheme 1.17). A novel synthesis of cyclopropane analogues utilising a sequential iodination/cyclisation strategy has been reported by Yu.<sup>45</sup> Alkyldimethyloxazoline derivatives **1.91** were shown to undergo Pd-catalysed diiodination of the *gem*-dimethyl substituents, directed by the oxazoline unit, to generate the corresponding diiodides **1.92**. These were subjected to radical cyclisation to afford the cyclopropane products in excellent yield (Scheme 1.18). Moreover, the oxazoline moiety could then be hydrolysed to give the corresponding cyclopropane carboxylic acid **1.94** over three steps.

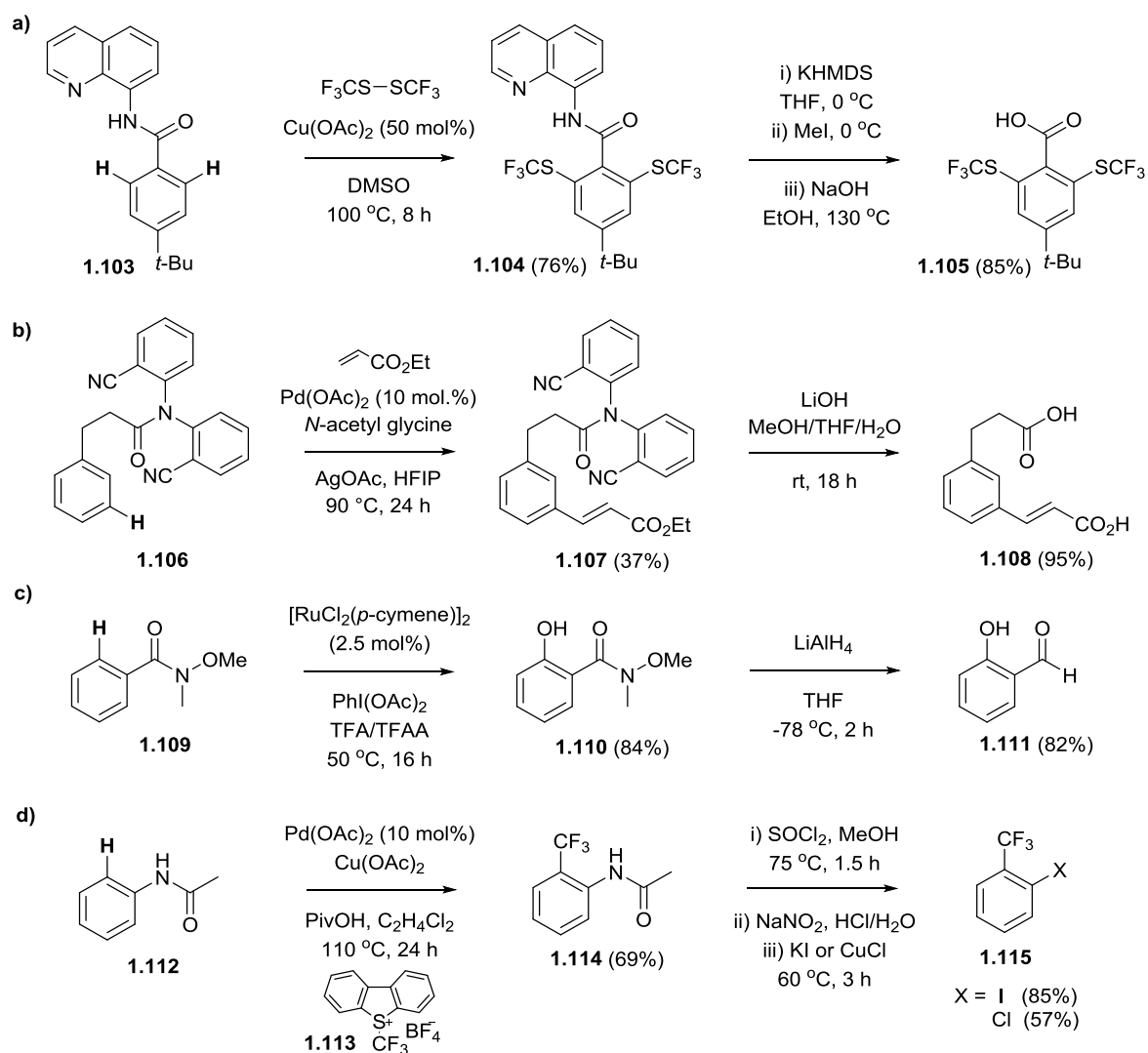


### 1.2.4 Directing group modifications

The use of directing groups in C-H functionalisation is a convenient way of controlling site-selectivity, but it is not always desirable to have these functional groups in the final products. The solution to this is to remove or modify the directing groups after the required C-H functionalisation step. A comprehensive account of this area is outside the scope of this review,<sup>46</sup> however some recent examples are worthy of note. Wu and co-workers made use of pyridine to direct the *ortho* arylation of carbazoles, before removing it to leave the unprotected, functionalised carbazole derivative **1.97**.<sup>47</sup> Arylation proceeded in good yield using Pd(OAc)<sub>2</sub> and the corresponding aryl BF<sub>3</sub>K salt as the coupling partner. Removal of the pyridine group was achieved in a two step protocol over 36 h using MeOTf and NaOH to give carbazole **1.97** in good yield (Scheme 1.19a). Similarly *N*-pyrimidyl substituents have been shown to facilitate arylation of indoles at C2.<sup>48</sup> The Ru-catalysed strategy employed aryl halides to access the C2 arylated indoles **1.99**, which could then be treated with NaOEt to remove the pyrimidine in a one-pot process to unprotected indole **1.100** (Scheme 1.19b). The pyridinesulfinyl directing group

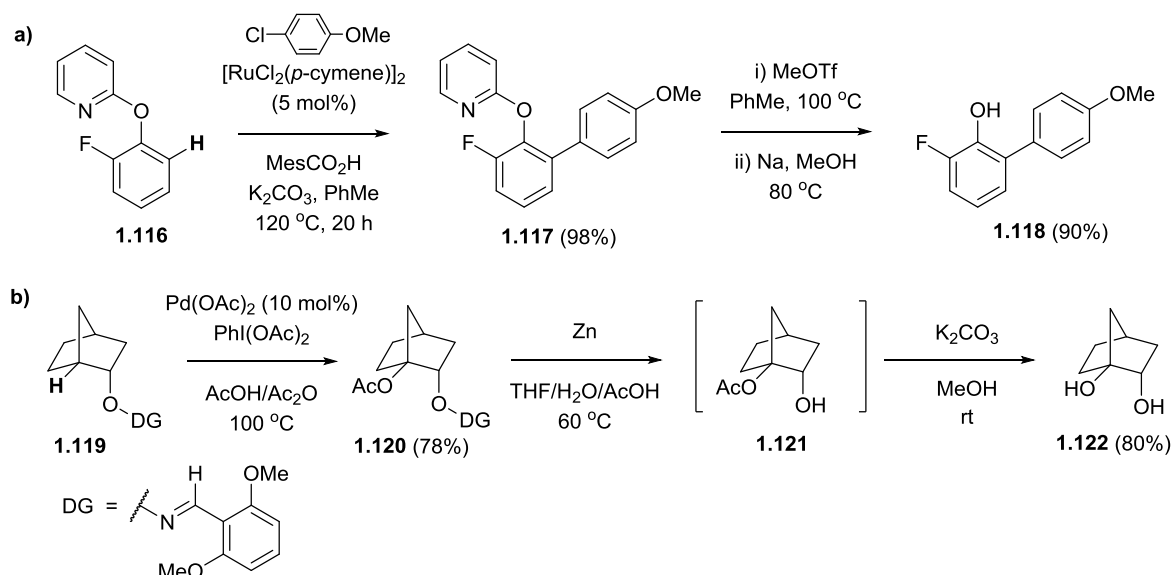


**Scheme 1.19** Use of traceless directing groups that can be completely removed



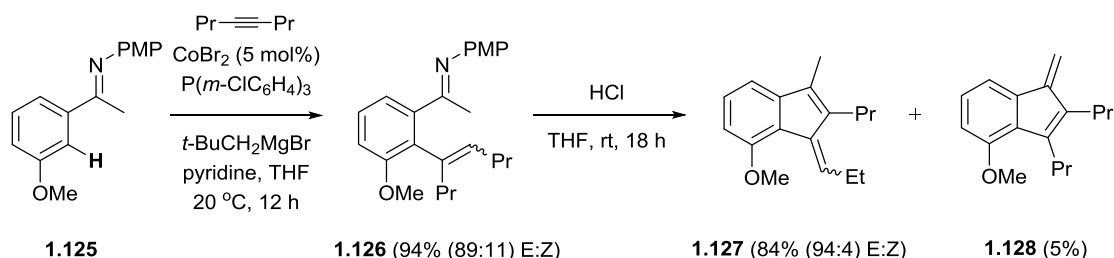
**Scheme 1.20** Amides as directing groups that can be modified to provide additional functionality

**1.6** discussed earlier can be removed in two steps using *n*-BuLi and  $\text{NH}_3\text{Cl}$ , but this time not just the pyridine, but also the heteroatom it is attached to can be removed to leave the functionalised carbon backbone **1.102** (Scheme 1.19c).<sup>19</sup> Some directing groups cannot be completely removed and leave a residual functional group which may itself be useful in synthesis. This is most common when using directing groups derived from amides. Daugulis et al. demonstrated the use of an amidoquinoline **1.103** to direct the Cu-catalysed *ortho* sulfenylation of arenes using disulfides.<sup>49</sup> Following the sulfenylation the amidoquinoline moiety was removed via methylation and hydrolysis to leave the corresponding carboxylic acid **1.105** (Scheme 1.20a). Baran also utilised a modification of this directing group to an aldehyde via DIBAL reduction, in the total synthesis of pipericyclobutanamide A (Scheme 1.8b).<sup>29</sup> Of similar note is an example of a diarylated



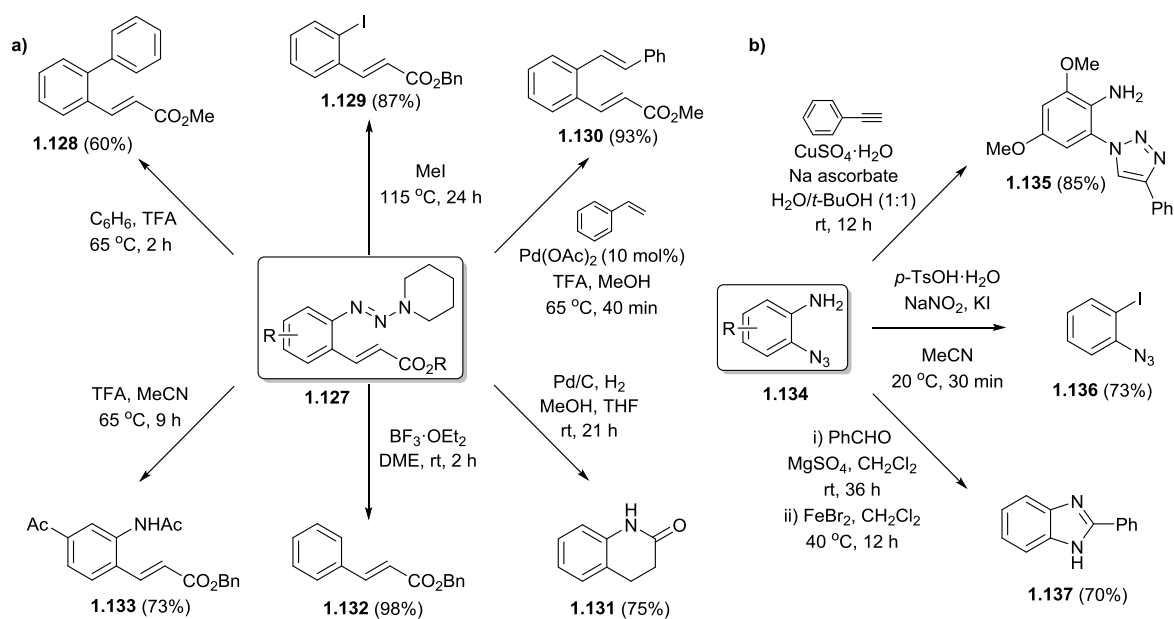
**Scheme 1.21** Directing groups that can be removed to reveal a free hydroxyl group

amide featuring a nitrile functionality that can direct the *meta* alkenylation of arenes.<sup>50</sup> Again subsequent hydrolysis of the resulting functionalised arene **1.107** affords the carboxylic acid **1.108** (Scheme 1.20b). Weinreb amides have been shown to act as good directing groups for the Ru-catalysed *ortho* hydroxylation of arenes.<sup>51</sup> The amides can then undergo reduction with LiAlH<sub>4</sub> to give access to a range of *ortho*-hydroxylated benzaldehydes **1.111** (Scheme 1.20c). Acetamido moieties have been used to direct a Pd-catalysed trifluoromethylation of arenes using **1.113**.<sup>52</sup> These can then be converted to the corresponding halides **1.115** in good yield over two steps for further use in synthesis (Scheme 1.20d). Ackermann disclosed the direct arylation of 2-phenoxy pyridine derivatives **1.116** catalysed by a ruthenium carboxylate complex.<sup>53</sup> Using aryl chlorides as coupling partners gave the *ortho*-arylated products in good yield and the pyridine functionality could be removed by subsequent heating with MeOTf, followed by sodium



**Scheme 1.22** Imine directing groups that can be further utilised in the synthesis of benzofulvenes

in MeOH, to leave the phenolic product **1.118** in excellent overall yield (Scheme 1.21a). This methodology has recently been extended to encompass alkenylations.<sup>54</sup> A particularly poignant example of oximes being used as directing groups has been developed by Dong et al.<sup>55</sup> With the purpose of employing the oxime **1.119** as a protected alcohol functionality, a second protected alcohol in the form of an acetoxy group was selectively installed at the  $\beta$ -position via Pd(OAc)<sub>2</sub> catalysed sp<sup>3</sup> C-H activation to give **1.120** (Scheme 1.21b). This leads to the formation of aliphatic 1,2-diols **1.122** that are chemically differentiated by virtue of their protecting groups, which can be sequentially removed in good yield to reveal the free OH groups as required. Perhaps the most powerful modification of a directing group from a synthetic perspective is one in which it can be transformed into functional groups that can be useful in the target compounds. Several nitrogen containing directing groups have been shown to be ideal to use for this purpose. Yoshikai and co-workers demonstrated the utility of imines in the synthesis of benzofulvenes **1.125** via a CDC with alkynes.<sup>56</sup> The *ortho*-directed CDC proceeded in good yield for both symmetric and unsymmetric internal alkynes, with the unsymmetric variants favouring the least hindered *E* isomers. Cyclisation under acidic conditions afforded benzofulvene **1.125** as a ratio of (94:4) (*E:Z*) isomers with trace amount of **1.126** also being observed (Scheme 1.22). Some directing groups can undergo divergent transformations to give a range of synthetically useful functional groups. Triazines have been successfully employed as directing groups for the Rh-catalysed alkenylation of arenes and can subsequently either be removed completely **1.132** or modified into several useful functionalities such as alkenes **1.130**, arenes **1.128**, halogens **1.129** or amides **1.133**, including one example of intramolecular cyclisation with the previously installed alkene to afford lactam **1.131** (Scheme 1.23a).<sup>57</sup> Tang and Jiao utilised an unprotected amine to direct the azidation of arenes under exceptionally mild reaction conditions.<sup>58</sup> Using a CuBr catalyst the group were able to affect C-H functionalisation with TMSN<sub>3</sub> at room temperature in 2 h, providing moderate to good yields of the corresponding *ortho* azidoaniline derivatives **1.134** (Scheme 1.23b). These were then further functionalised by modification of either the amine, azide or both to give triazole **1.135**, iodide **1.136** or benzimidazole **1.137**.



**Scheme 1.23** Versatile divergent modifications of triazines and amines as directing groups

### 1.3 Summary

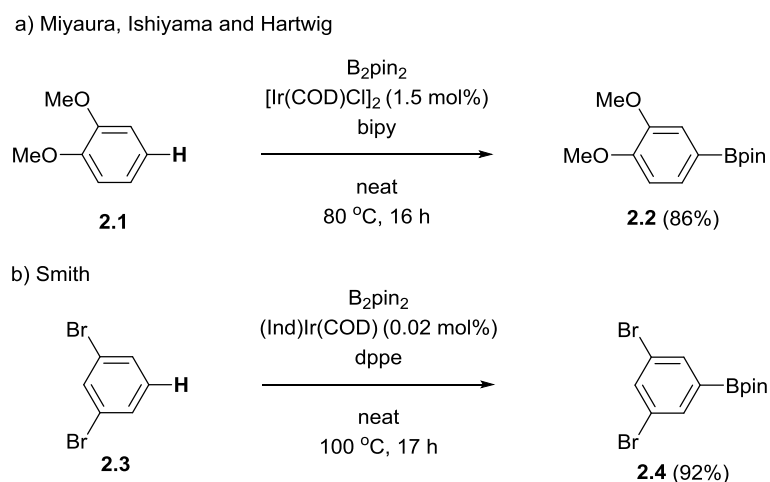
In summary sequential reaction protocols that make use of catalytic C-H functionalisation processes have been widely explored in recent years, in an effort to develop more efficient synthetic methodologies, with significant advances in iterative C-H functionalisations, as well as in combination with other synthetic transformations. The ability to control regioselectivity in C-H functionalisation processes has led to a number of examples of highly substituted benzene derivatives and complex polycyclic and heterocyclic systems being synthesised using sequential methodologies. Sequential C-H functionalisations have also found use in the synthesis of natural products and a pharmaceutical candidate, the synthetic route to the latter proving more efficient with fewer reaction steps and producing less waste than the one previously devised. Cross-couplings too can play a role in providing additional functionality, in a sequential fashion and accessing structures not yet available via direct C-H functionalisation. One of the criticisms of chelation-assisted C-H functionalisation is the need to use directing groups that are oftentimes undesirable or of no use in the target compounds. Removable directing groups can go some way towards alleviating this concern by leaving the functionalised molecular scaffold free from the directing group, however current applications of these are limited and in need of significant development if they are to

become commonplace. A more atom-efficient, albeit more complex, strategy is to utilise a modifiable directing group that can be transformed into a useful functionality and incorporated into the target molecule as part of the reaction sequence. Overall, sequential processes that make use of C-H functionalisations show significant promise for synthetic chemistry and can prove to be more efficient than conventional synthetic transformations, as routes to existing complex molecular motifs, as well as providing access to new and more interesting ones.

## 2. Expanding the Scope of Ru-catalysed *meta* C-H Functionalisation

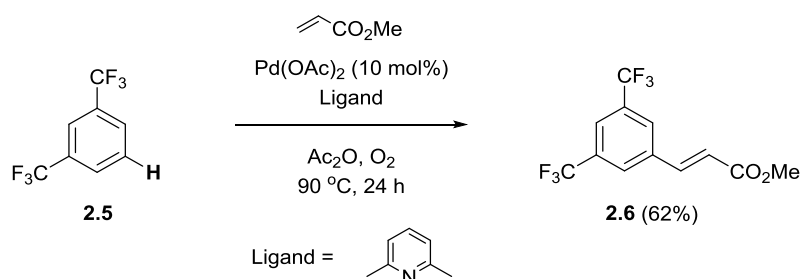
### 2.1 *meta*-Selective Aromatic C-H Functionalisations

Chelation-assisted C-H activation is a common method for controlling the selectivity of direct C-H bond functionalisation processes, particularly in arenes.<sup>14</sup> The vast majority of these methodologies are used to functionalise the position *ortho* to the directing group on the aryl ring.<sup>15</sup> Recently there have been a number of examples of catalytic functionalisation of the *meta* position using several different transition metal catalysts and coupling partners. Some of the earliest examples of *meta* C-H functionalisations were Ir-catalysed borylations of arenes using pinacol boranes, reported independently by Smith<sup>59</sup> and Miyaura, Ishiyama and Hartwig.<sup>60</sup> These protocols were shown to be effective for the *meta* borylation of 1,3-disubstituted arenes, with functionalisation occurring at the least hindered site (Scheme 2.1). It was also noted the selectivity was controlled predominantly by the need to minimise steric interactions and not by electronic factors, as mono-substituted arenes gave mixtures of both *meta* and *para* borylated products. Hartwig went on to make use of these meta borylated arenes to introduce additional functionality such as halides<sup>41, 42</sup> and alkyl, alkenyl and benzyl substituents.<sup>36</sup> Snieckus and Marder also demonstrated further functionalisation of these intermediates by introducing a variety of aryl groups via Suzuki coupling.<sup>34</sup>

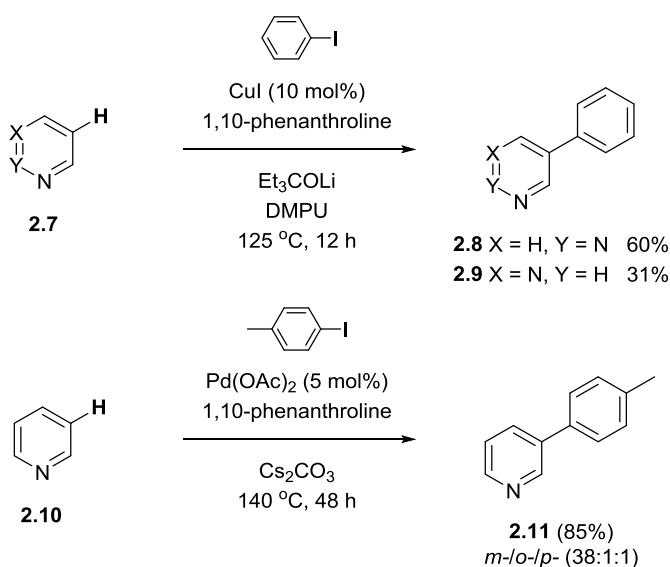


**Scheme 2.1** Ir-catalysed *meta* borylation

Yu illustrated an example of the *meta* alkenylation of arenes without an intermediary borylation step (Scheme 2.2).<sup>22</sup> Similar selectivity was observed with mono-substituted arenes giving mixtures of regioisomers, favouring the *meta* products. Arylation of heteroaromatic substrates including pyridine, pyrimidine and pyridiazine have been developed by Dagulis<sup>61</sup> and Yu,<sup>62</sup> using Cu and Pd catalysts respectively and both aided by the use of 1,10-phenanthroline as a ligand (Scheme 2.3). The latter report noted that the observed selectivity was due to initial chelation of Pd to the heteroatom, which then directs oxidative addition at C3 and facilitates arylation. Larossa described a pseudo-*meta* arylation strategy employing a removable carboxylic acid chelating group to direct functionalisation *ortho* to the acid, which is subsequently removed via decarboxylation mediated by a silver salt, to reveal the *meta* functionalised product (Scheme 2.4).<sup>63</sup>

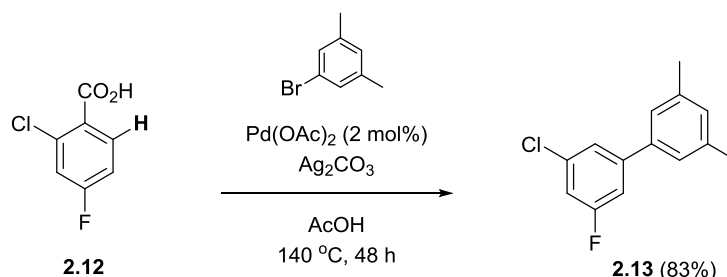


**Scheme 2.2** Pd-catalysed *meta* alkenylation



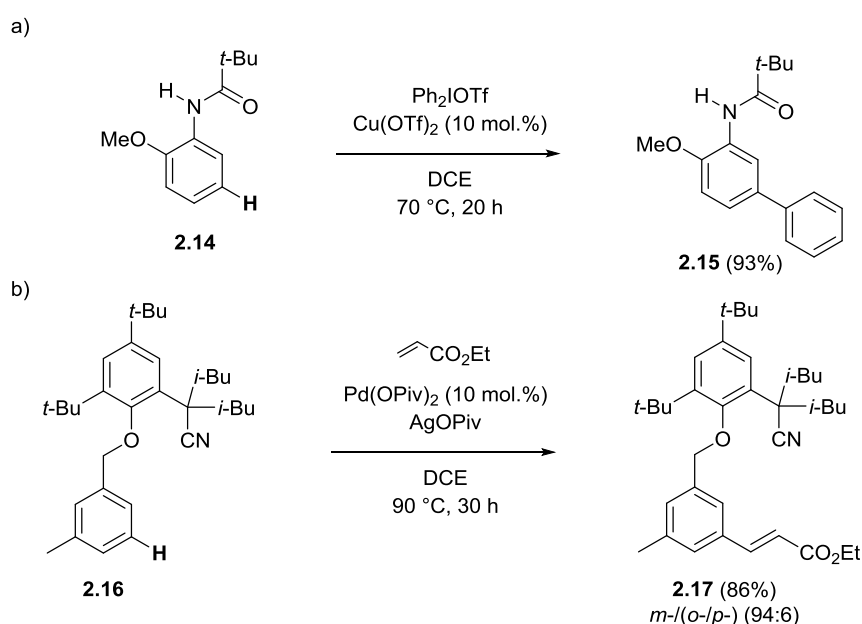
**Scheme 2.3** *meta* arylation of heteroaromatics





**Scheme 2.4** Carboxylic acid-directed pseudo-*meta* arylation

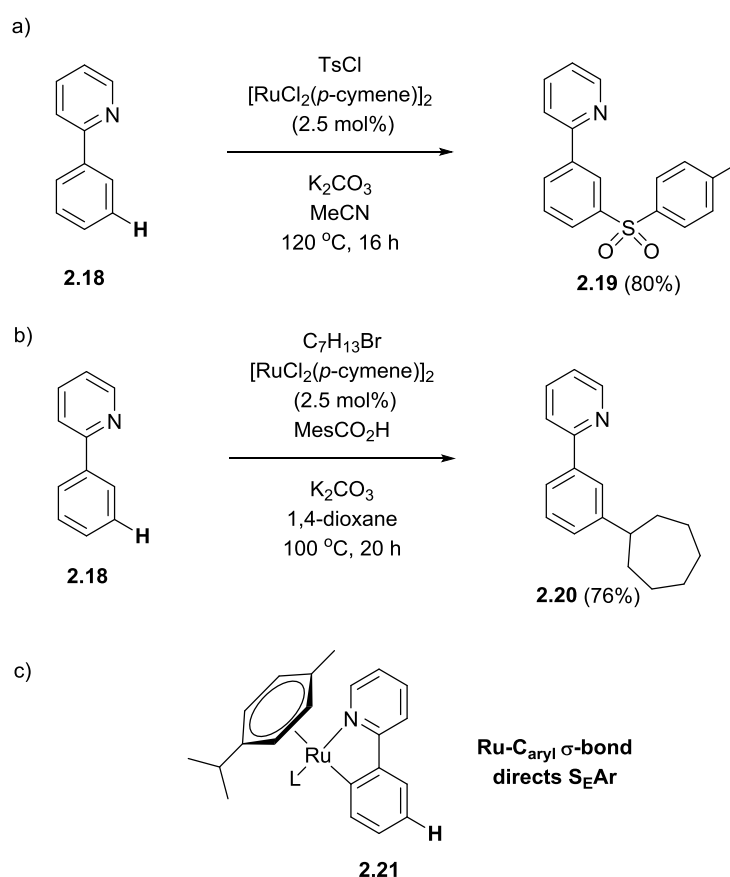
Phipps and Gaunt developed a direct *meta* arylation of pivanilide derivatives using  $\text{Cu}(\text{OTf})_2$  to catalyse coupling with diaryliodonium salts (Scheme 2.5a).<sup>64</sup> The group went on to extend this methodology for use with  $\alpha$ -aryl carbonyl compounds, which have much less electron density, highlighting the importance of the carbonyl group in overcoming inherent electronic bias.<sup>20</sup> Originally, it was proposed that both examples proceeded via a dearomatising ‘oxy-cupration’ step, however upon further investigation it was found that the same selectivity could be achieved in the absence of copper at slightly elevated temperatures, suggesting that the  $\text{Cu}(\text{OTf})_2$  only serves to activate the diaryliodonium salt toward coupling and the observed *meta* selectivity is predominantly controlled by the carbonyl functionality. A formal chelation-assisted *meta* alkenylation protocol, published by Yu and co-workers, made use of a tethered nitrile group to directly activate remote *meta* C-H bonds by virtue of favourable steric interactions (Scheme 2.5b).<sup>50</sup> The length of the tether was found to be crucial to avoid activation of the *ortho* position.



**Scheme 2.5** Versatile *meta* functionalisation of arenes

Recent work in the Frost group has focused on the development of a chelation-assisted *meta* sulfonation methodology, catalysed by  $[\text{RuCl}_2(p\text{-cymene})]_2$ .<sup>31</sup> A range of functionalised sulfones were obtained in good yield, although the scope was limited to using sulfonyl chlorides as electrophiles and pyridine derivatives as the chelating group (Scheme 2.6a). Ackermann reported an expansion of this methodology to encompass *meta* alkylation using secondary alkyl halides and a limited number of other nitrogen-containing heterocyclic directing groups (Scheme 2.6b).<sup>65</sup> Both of these protocols have been shown to proceed via Ru-directed  $\sigma$ -activation of cyclometalated intermediate **2.21** (Scheme 2.6c)

This chapter deals with work on the extension of this Ru-catalysed  $\sigma$ -activation methodology to try and encompass additional directing groups and electrophiles, with the potential to provide access to new and interesting *meta* functionalised arenes.

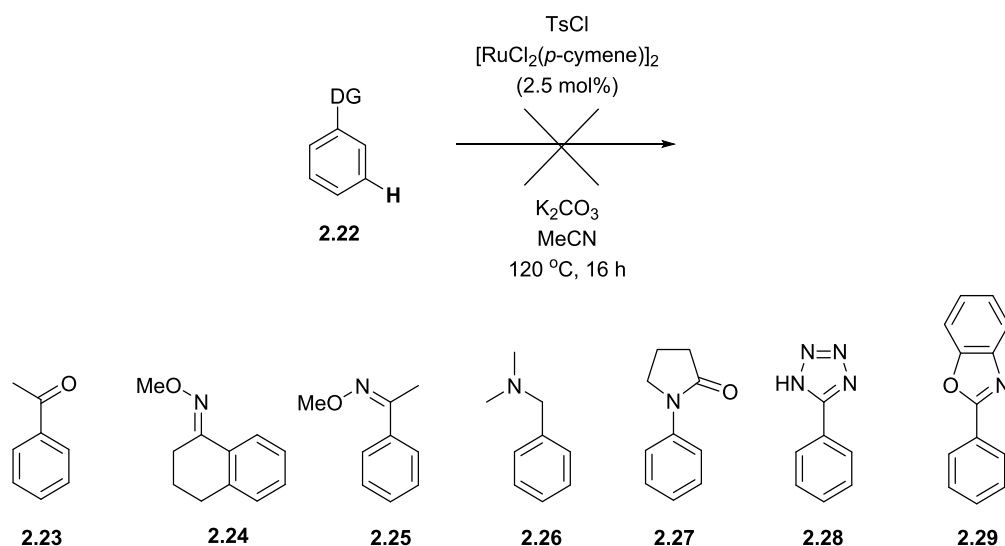


**Scheme 2.6** Ru-catalysed sulfonation and alkylation of 2-phenylpyridines

## 2.2 Alternative Directing Groups

Pyridine has been widely used as a directing group for both *ortho* and *meta* C-H functionalisations with a variety of catalysts and coupling partners. This is primarily due to the ease with which it can undergo both cyclometalation and demetalation during the catalytic cycle. If a directing group is not able to form a stable cyclometalated species or, more commonly for *ortho* functionalisations, if the cyclometalated intermediate is too stable and does not allow functionalisation of the activated C-H bond, then the catalytic cycle is disrupted and functionalisation does not occur. However, 2-phenylpyridines are not particularly useful in synthesis, outside of being model substrates for the development of new C-H functionalisation methodologies, and so there is a pressing need to utilise other functional groups to direct these processes.

To this end several other chelating groups commonly used for *ortho* functionalisation processes were investigated for use within the *meta* sulfonation protocol. These included ketones, oximes and amines, as well as heterocycles such as tetrazole, benzoxazole and pyrrolidinone (Scheme 2.7). Unfortunately none of these chelating groups showed any sign of being able to direct the Ru-catalysed *meta* sulfonation and no other *ortho* functionalised products were observed, with only starting material returned in each case.



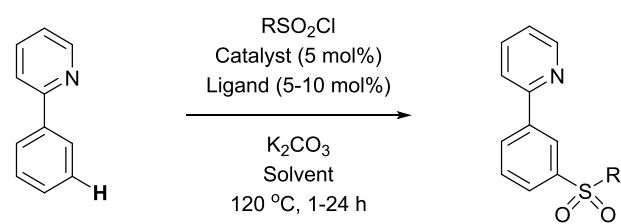
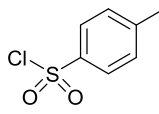

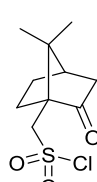
**Scheme 2.7** Directing groups investigated in the meta sulfonation protocol

## 2.3 Experimental Design

The lack of positive results obtained from the study of alternative directing groups illustrated how sensitive the methodology was to any deviations from the reported conditions. It quickly became apparent that a new, more robust, set of experimental conditions may be necessary in order to improve the scope of the methodology and make it more synthetically useful.

The use of ‘design of experiment’ (DoE) principles can significantly reduce the time and resources needed for the optimisation of new synthetic methodologies and particularly catalytic processes, compared to the conventional ‘one variable at a time’ approach.<sup>66</sup> By using dedicated software the importance of each variable in the reaction can be assessed simultaneously and significantly reduce the number of permutations needing to be run to determine the optimal combination.

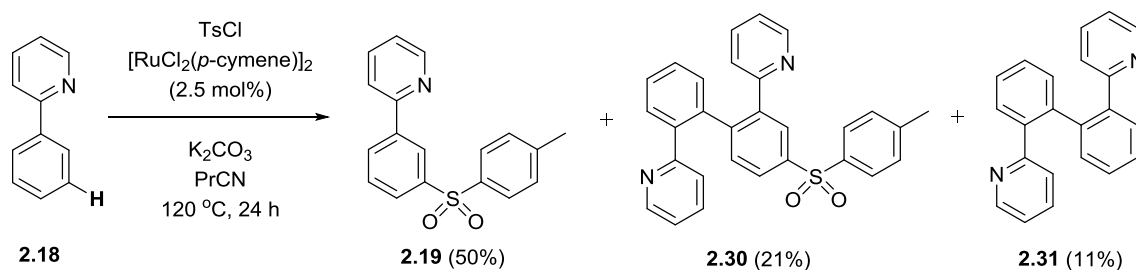
**Table 2.1** Variables used as part of the experimental design

|  |                                      |                           |               |
|--|--------------------------------------|---------------------------|---------------|
| Electrophiles  | Catalysts                            | Ligands                   | Solvents      |
|   | $[\text{RuCl}_2(p\text{-cymene})]_2$ | BINAP                     | PrCN          |
|  | $\text{Pd}(\text{OAc})_2$            | (+)-DIOP                  | cyclohexanone |
|  | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DEPE                      | 3-pentanone   |
|  | $[\text{Ir}(\text{COD})\text{Cl}]_2$ | DPPE                      | DMA           |
|   | CuI                                  | $\text{P}(t\text{-Bu})_3$ | PhCN          |
|  | $\text{NiCl}_2$                      | X-Phos                    | PhCl          |
|   |                                      | $\text{P}(\text{EtCN})_3$ | BuOAc         |
|  |                                      | PhPEt <sub>2</sub>        | Diglyme       |
|  |                                      | Triphos                   | PhOMe         |

In collaboration with CatSci, an SME that specialises in the use of DoE to optimise catalytic processes, an experimental design was conceived to encompass a wide range of possibilities for several of the key variables, including catalyst, ligand, solvent and temperature. Alternative electrophiles were also included in the design to try and widen the scope of the protocol to include alkylsulfonyl chlorides as well. The ligands and solvents were chosen using a principle component analysis (PCA) technique which maps hundreds of known compounds according to their properties, in a multidimensional 'chemical space', and allowing a selection to be taken from across the chemical space and enabling the experimental design software to determine which specific properties are important for the reaction.<sup>66</sup> The experimental design consisted of 25 combinations of the variables, which were used for each catalyst in turn totalling 150 reactions in all, that covered potentially millions of possible permutations in an effort to see whether the standard conditions for the *meta* sulfonation could be improved.

Remarkably, no *meta*-sulfonated products were seen in any of the samples other than the control reactions, which were run under standard conditions with the exception of a solvent switch from MeCN to PrCN, due to the necessity to work in unpressurised reaction vessels. Furthermore, no reaction products were found at all in any samples except those containing ruthenium.

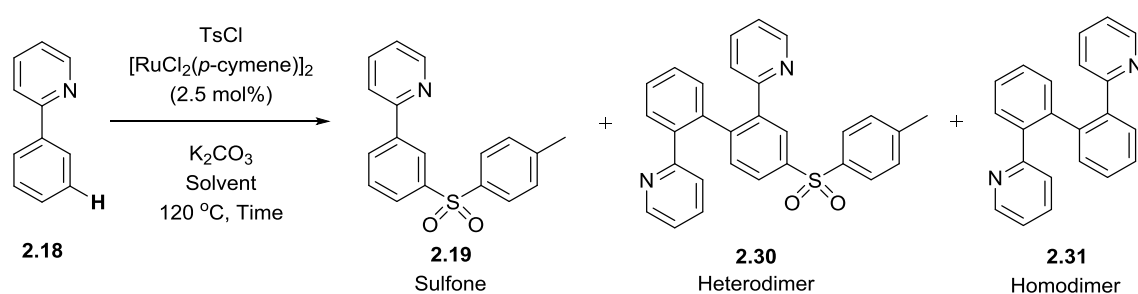
The silver lining in this work was revealed upon analysis of the control sample by LC-MS, an analytical technique which had not so far been used in conjunction with this methodology. It revealed the presence of two previously unseen byproducts; dimeric species **2.30** and **2.31** in 21% and 11% conversion respectively, along with 18% unreacted starting material. Upon closer inspection it emerged that dimer **2.31** was present in trace quantities of 4-5% in every sample run using the  $[\text{RuCl}_2(p\text{-cymene})]_2$  catalyst.



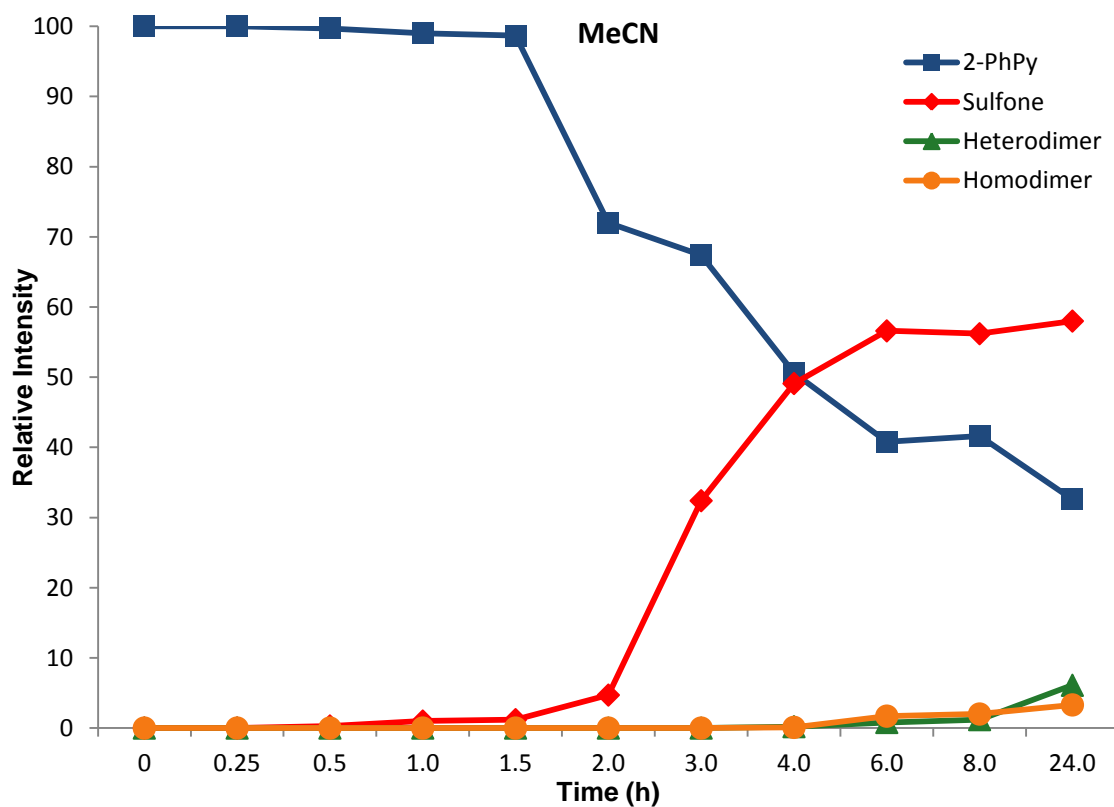
**Scheme 2.8** Dimeric byproducts identified by LC-MS

## 2.4 Dimeric Byproducts

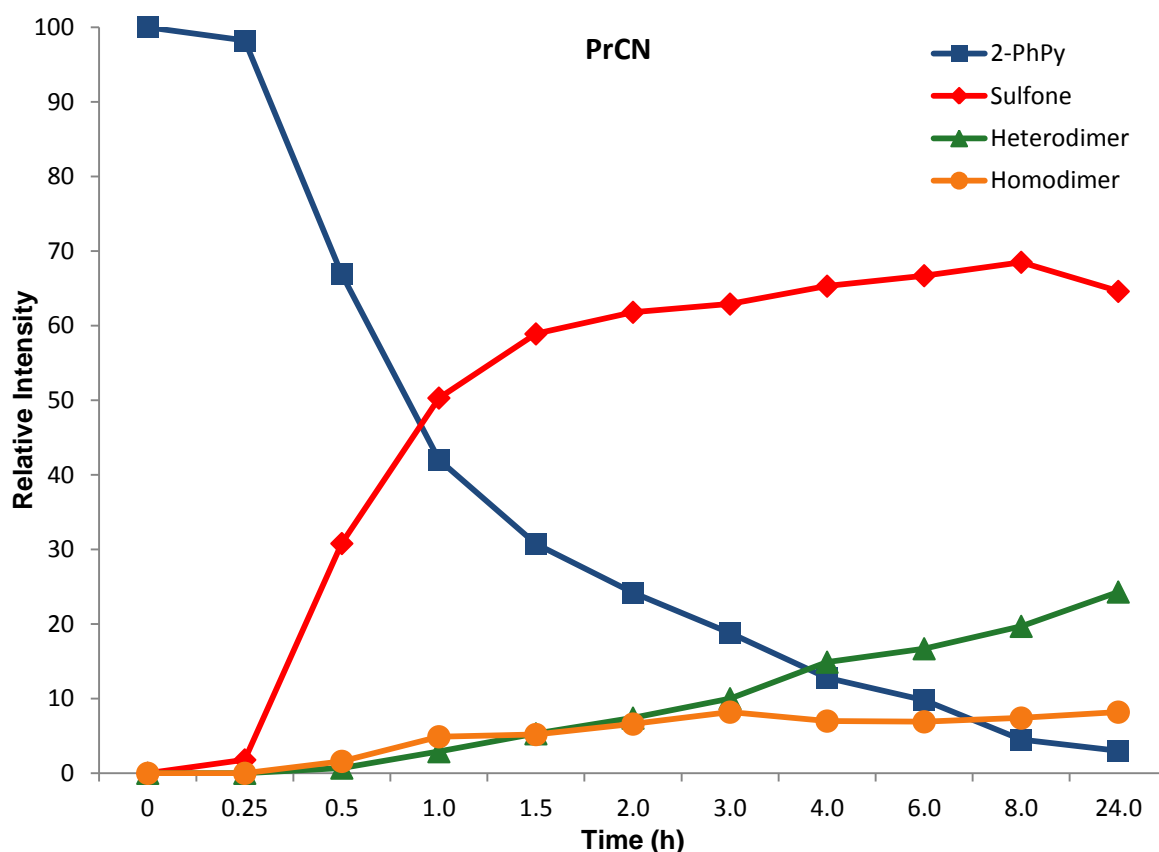
The elucidation of these, previously unknown, byproducts warranted further investigation into their formation. It was unclear whether they were a result of the new solvent (PrCN) having a higher boiling point and thus being able to reach higher temperatures during the reaction or whether they were also present under the standard conditions using MeCN. To test these hypotheses, work conducted by Dr Patricia Marce-Villa sought to collect LC-MS data over a 24 h period in each solvent and



**Scheme 2.9** Amounts of sulfone, heterodimer and homodimer formed over 24 h

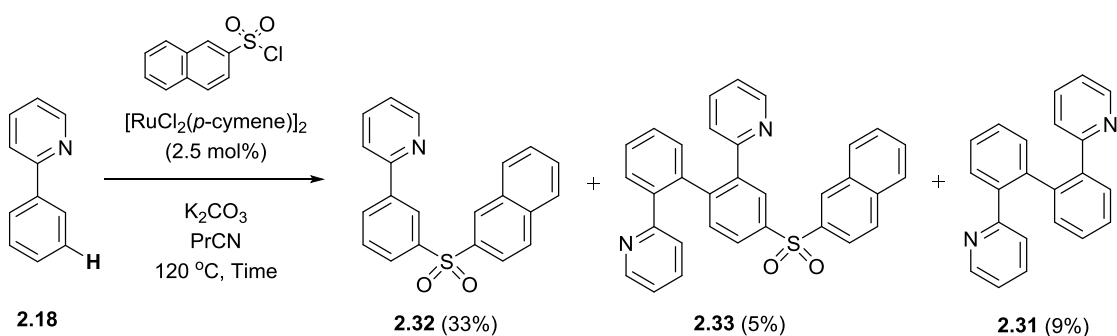


**Figure 2.1** Product formation over 24 h in MeCN



**Figure 2.2** Product formation over 24 h in PrCN

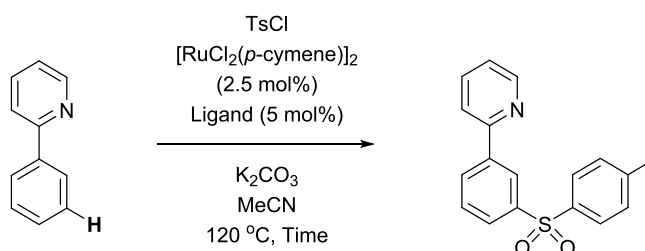
the amounts of 2-phenylpyridine, sulfone and the two byproducts, now termed ‘heterodimer’ **2.30** and ‘homodimer’ **2.31**, present in each sample were measured and collated (Figures 2.1 and 2.2). From these figures several important conclusions can be drawn. First, that both solvents give more or less the same conversion to *meta* sulfone **2.19** over 24 hours. The second observation is that there is a relatively long induction time of 2 h when using the standard conditions in MeCN. Using PrCN the induction time is reduced to 15 min. Thirdly, the amount of both dimer byproducts is significantly higher in PrCN than MeCN, which is possibly why they hadn’t been discovered prior to this work. Both the heterodimer and homodimer do not begin to form until after the *meta* sulfone, suggesting that the dimerisation step is significantly slower than the sulfonation. This observation is also supported by the trace amounts of homodimer seen in the samples containing ruthenium, but *not* sulfone, within the experimental design work run in PrCN.



**Scheme 2.10** Isolated yields of sulfone and dimeric byproducts using 2-naphthylsulfonyl chloride

As yet, the dimers had only been identified using LC-MS and not physically isolated as reaction products, so this was the next target. Perhaps surprisingly, the only reaction in which the heterodimer **2.33** could be isolated was when 2-naphthylsulfonyl chloride was used as the coupling partner, and in a lower yield than the homodimer, possibly due to fact that 2-naphthylsulfonyl chloride is substantially harder to couple.

**Table 2.2** Yields of sulfone obtained using different pyridyl-type ligands



| Entry            | Ligand | Yield (%) |
|------------------|--------|-----------|
| 1 <sup>[a]</sup> |        | -         |
| 2                |        | 0         |
| 3                |        | 55        |

[a] Upon addition of the ligand to the reaction mixture a black precipitate was formed



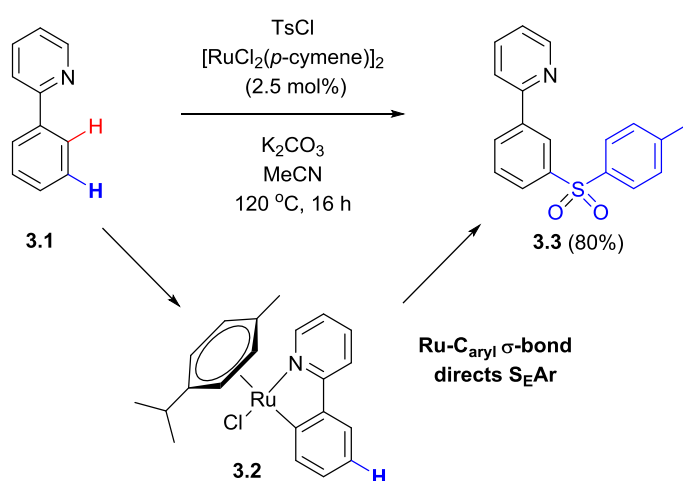
Despite the LC-MS data suggesting that the formation of the majority of the dimeric species occurred after the formation of the sulfone, it was still possible that trace amounts of the homodimer could be forming prior to the sulfone, acting as a ligand and forming the active catalytic species in situ to promote *meta* sulfonation. To see if this theory was at all credible, an experiment was conducted in which 5 mol% of the homodimer **2.31** was added at the start of the reaction to see if this resulted in a higher yield of the sulfone **2.19**. Two other common pyridyl species were also tested; pyridine and bipyridyl. The reaction using pyridine turned black immediately after its addition, likely due to reaction with the sulfonyl chloride and was not taken any further. Bipyridyl proceeded to inhibit the reaction completely with only starting material returned and addition of the homodimer at the start of the reaction did not improve the yield of the sulfone above the levels observed previously, suggesting that it is not part of the active catalytic species.

## 2.5 Conclusions

In conclusion, in an effort to expand the applicability and substrate scope of the *meta* sulfonation protocol several new directing groups and electrophiles were trialled under the standard reaction conditions and attempts were also made to investigate a wide range of other experimental conditions – including catalysts, ligands and solvents – using an experimental design strategy. Ultimately, no extensions or improvements to the initial methodology could be made, however, during LC-MS analysis it was discovered that two, previously unseen, dimeric byproducts are formed during the reaction which were isolated and characterised. They were found to form after the primary *meta*-sulfonated product and no evidence of their involvement in the catalytic cycle was found.

### 3. Sequential C-H Functionalisations of 2-Phenylpyridines

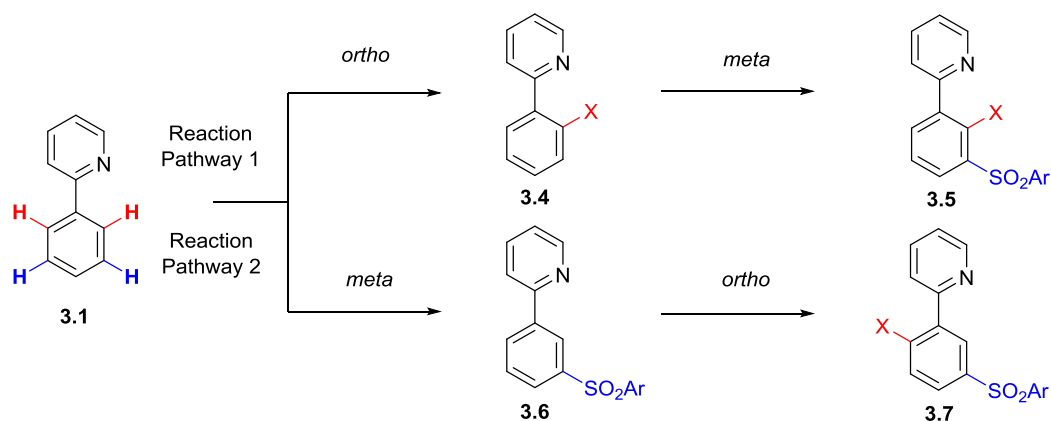
The catalytic  $\sigma$ -activation methodology explored in Chapter 2 (Scheme 3.1) provides a unique mechanism of operation with *meta* selectivity and as such, holds significant potential for use in sequential processes, complementing other examples of sequential C-H functionalisation strategies discussed in Chapter 1. This chapter focuses on the development of a sequential regioselective C-H functionalisation protocol facilitated by the Ru-catalysed  $\sigma$ -activation protocol.



**Scheme 3.1** Ru-catalysed *meta* sulfonation via cyclometalated intermediate **3.2**

#### 3.1 Complementary Regioselectivity

The inherent difference between this *meta* C-H bond functionalisation methodology, requiring cyclometalation at the *ortho* position before directing remote functionalisation of the *meta* position on the opposite face of the aromatic ring, as opposed to direct activation of the *ortho* position displayed in the majority of cases of C-H functionalisations with transition metals, gives rise to the possibility that regioisomers of highly substituted 2-phenylpyridine derivatives could be obtained via sequential C-H functionalisation strategies, that utilise the *ortho* and *meta* protocols in a different order. To this end, two complementary reaction sequences were devised that were anticipated to be able to furnish opposing regioisomers selectively and hence could be of significant synthetic value (Scheme 3.2). Reaction pathway 1 consists of a standard chelation-assisted *ortho* C-H functionalisation to give **3.4**, which would then be subjected to the Ru-catalysed *meta*-



**Scheme 3.2** Proposed regioselectivity of two opposing reaction sequences.

selective sulfonation protocol. Due to the necessity of having to cyclometalate prior to sulfonation of the *meta* C-H bond, the Ru catalyst in the second step would be forced to undergo oxidative insertion into the remaining unfunctionalised *ortho* C-H bond and direct the electrophile *ortho* to the previous substituent (in this case shown as 'X') giving the C8-C9 substituted isomer **3.5**.

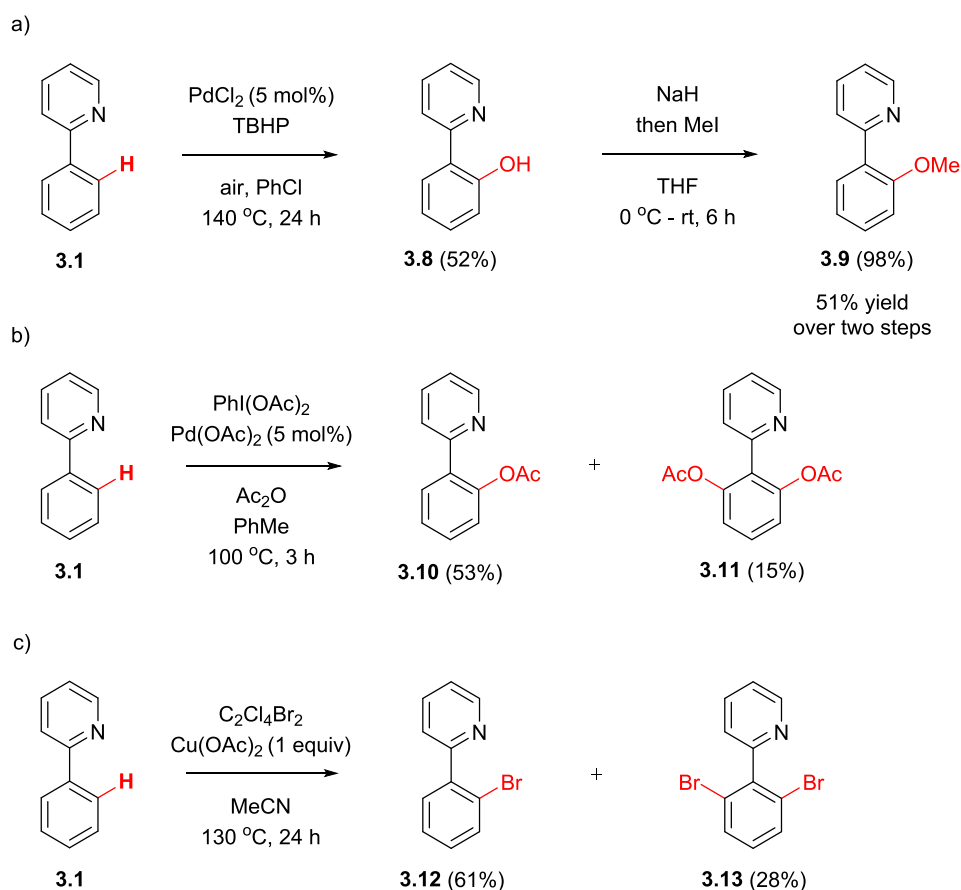
Reaction pathway 2 however, employs the opposite strategy of first functionalising the *meta* position to give **3.6**, followed by *ortho* functionalisation which, following literature precedent, would be expected to occur at the least sterically hindered site *para* to the previous substituent to give the C8-C11 substituted isomer **3.7**.<sup>67</sup> To test this hypothesis, both reaction pathways were investigated in an effort to develop complimentary sequential functionalisation methodologies.

## 3.2 Reaction Pathway 1

### 3.2.1 *ortho* C-H functionalisation

A wide range of chelation-assisted *ortho* C-H functionalisation reactions are present in the literature, of which three were initially chosen to explore the potential range of steric and electronic properties that were compatible with reaction pathway 1.

A methoxy group was the first *ortho* substituent to be chosen, as it would give the best chance of minimising any unfavourable steric interaction between itself and the pyridine



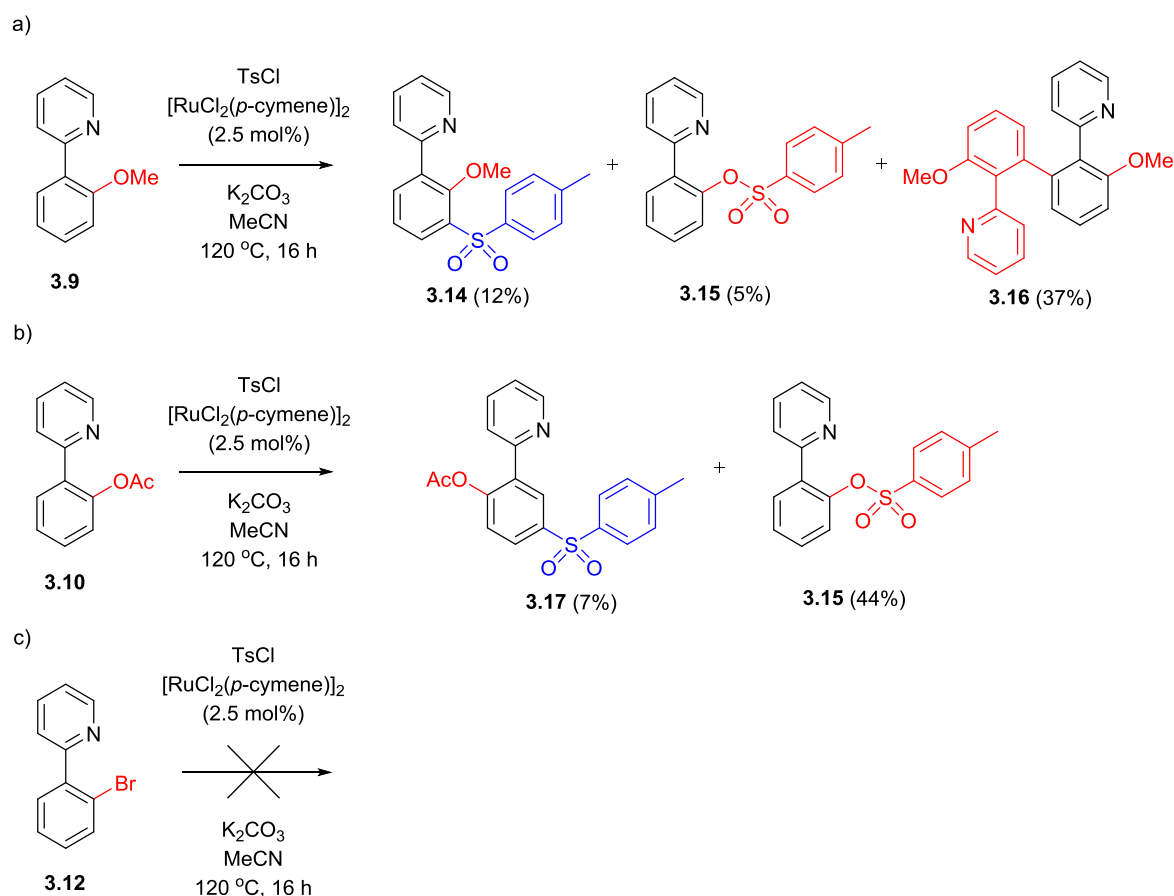
**Scheme 3.3** Products obtained from three different *ortho* functionalisation reactions

ring, whilst also providing an *ortho* directing effect and further activate the *meta* position to functionalisation. Direct *ortho* alkoxylation of 2-phenylpyridine is currently unknown in the literature and attempts to modify alkylation protocols reported for other chelating groups were unsuccessful.<sup>68-70</sup> The next best approach was to utilise a sequential strategy to first install a hydroxyl group in the *ortho* position,<sup>71</sup> followed by a methylation using methyl iodide (Scheme 3.3a). This gave the required compound **3.9** in a reasonable overall yield of 51%. The other substituents to be chosen were acetoxy and bromo functionalities, which would each provide an increase in steric interaction with the pyridine group and a decrease in electron density, thus reducing any secondary directing effects. Both acetoxylation and bromination were achieved using reported literature methods, with palladium<sup>72</sup> and copper<sup>73</sup> catalysts respectively. Acetoxylation proceeded readily with a reduction in the amount of both  $\text{PhI(OAc)}_2$  and  $\text{Ac}_2\text{O}$  used, to minimise formation of unwanted disubstituted product **3.11**. Similarly, bromination benefitted from a modification to the bromine source, swapping  $\text{C}_2\text{H}_2\text{Br}_4$  for  $\text{C}_2\text{Cl}_4\text{Br}_2$ , to improve its

electrophilicity and thus make it easier to form the postulated  $\text{CuBr}_2$  intermediate. As a consequence this gave an improved yield of 61% monobrominated product **3.12**, compared with 40% obtained using the existing reagent, again with a small amount of a disubstituted byproduct **3.13**.

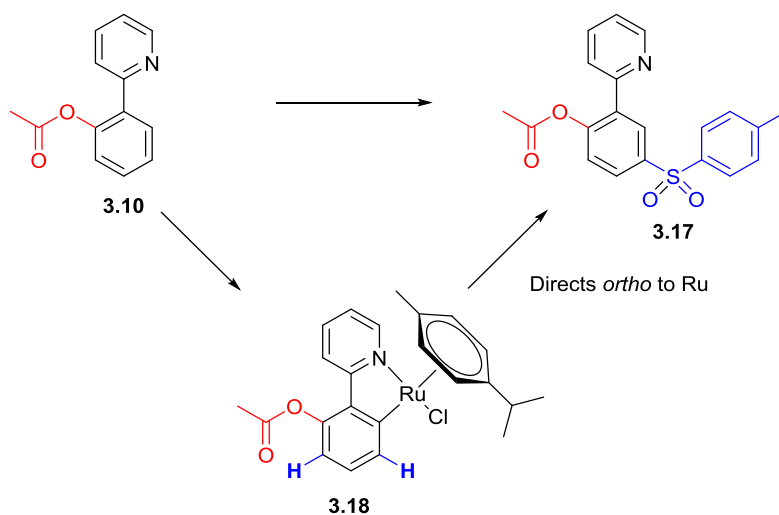
### 3.2.2 *meta* C-H functionalisation

With each of the required monosubstituted 2-phenylpyridine derivatives in hand, they were then taken through to the next stage of reaction pathway 1 and subjected to the now familiar Ru-catalysed *meta* sulfonation conditions. Scheme 3.4 shows the mix of products and regioselectivities obtained for each *ortho* substituent. The *ortho*-methoxy derivative **3.9** gave a mixture of three products, one of which was the *meta*-sulfonated compound **3.14** with the anticipated regioselectivity for the C8-C9 isomer, however only

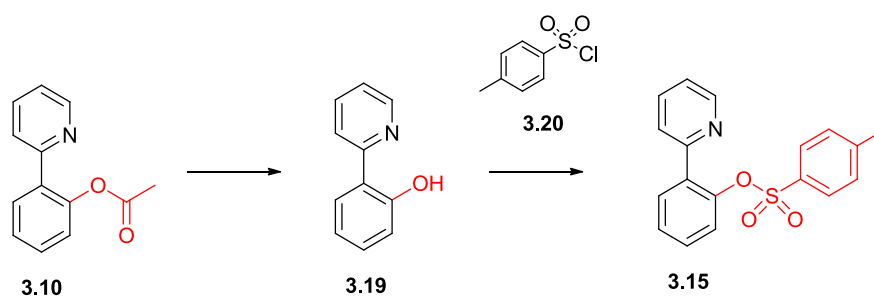


**Scheme 3.4** Regioselectivity of products obtained from reaction pathway 1

in low yield (12%). By far the major product from this reaction was dimeric species **3.16** which was obtained in 37% yield. Tosyloxy derivative **3.15** was also isolated as another byproduct, although only in trace amounts. For the *ortho*-acetoxy derivative **3.10** a sulfonated product was again observed, however this time with the opposite regioselectivity, as the C8-C11 substituted isomer **3.17**. This result was not totally unexpected, as the substantial decrease in *ortho*-directing ability and increase in steric bulk of the acetoxy group makes the C8-C9 isomer significantly harder to form. Moreover, during the course of this investigation, Ackermann also published observations of the formation of small amounts of these isomers when using *ortho*-substituted 2-phenylpyridines and demonstrated that, while the cyclometalated ruthenium intermediate predominately directs functionalisation at C9, it is also capable of directing functionalisation at C11. In this case the steric hindrance from the acetoxy substituent in intermediate **3.18** shuts down sulfonation at C9 completely so that only sulfonation at C11 is possible (Scheme 3.5).<sup>65</sup> Interestingly, the tosylated byproduct **3.15** was again observed, this time in much higher yield. No dimeric species were found, possibly due to competition with **3.15**, and also the increased steric hinderance of the acetoxy group making it unfavourable. In the case of the *ortho*-bromo substituent **3.12** the steric bulk is increased even further, thus cyclometalation is more difficult, and any secondary directing effects are removed, both hindering product formation and only starting material was returned. A possible mechanism for the formation of the unexpected tosylated byproduct **3.15** is given in Scheme **3.6** – via the unprotected phenol derivative **3.19** – which could be formed by hydrolysis of **3.10**



**Scheme 3.5** Sulfonation directed *ortho* to cyclometalated ruthenium

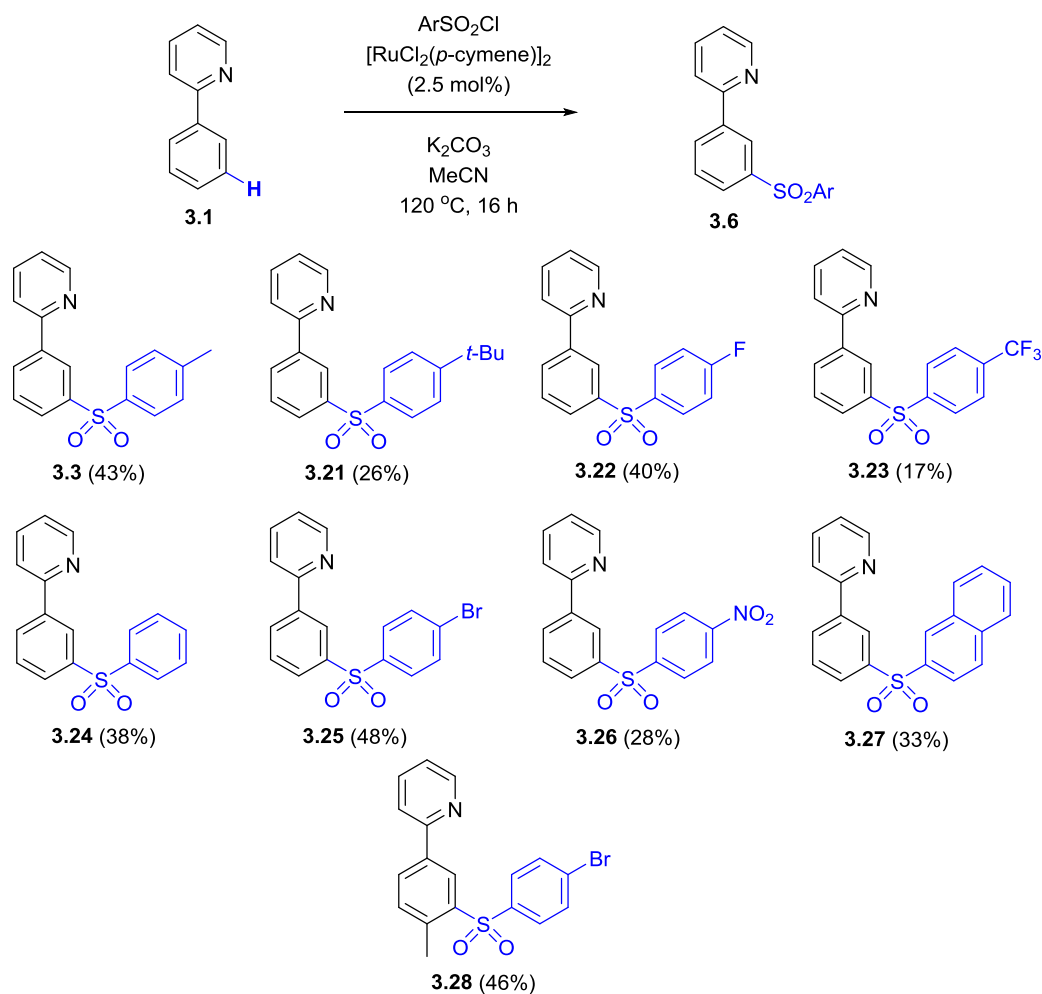


**Scheme 3.6** Possible mechanism for the formation of byproduct **3.15**

### 3.3 Reaction Pathway 2

#### 3.3.1 *meta* C-H functionalisation

Reaction pathway 2 consisted of first functionalising the *meta* position of 2-phenylpyridine using the Ru-catalysed sulfonation methodology, followed by subsequent functionalisation of the *ortho* position, in an effort to explore the regioselectivity and synthetic potential and of this strategy. A range of *meta*-sulfonated 2-phenylpyridines were successfully synthesised in moderate to good yield using the standard Ru-catalysed methodology (Scheme 3.7). These included a variety of substituents on the aryl ring of the sulfone including; bromo, fluoro, *t*-butyl, nitro and trifluoromethyl groups, as well as an example containing a naphthalene functionality. These were then taken forward to the next stage of reaction pathway 2.



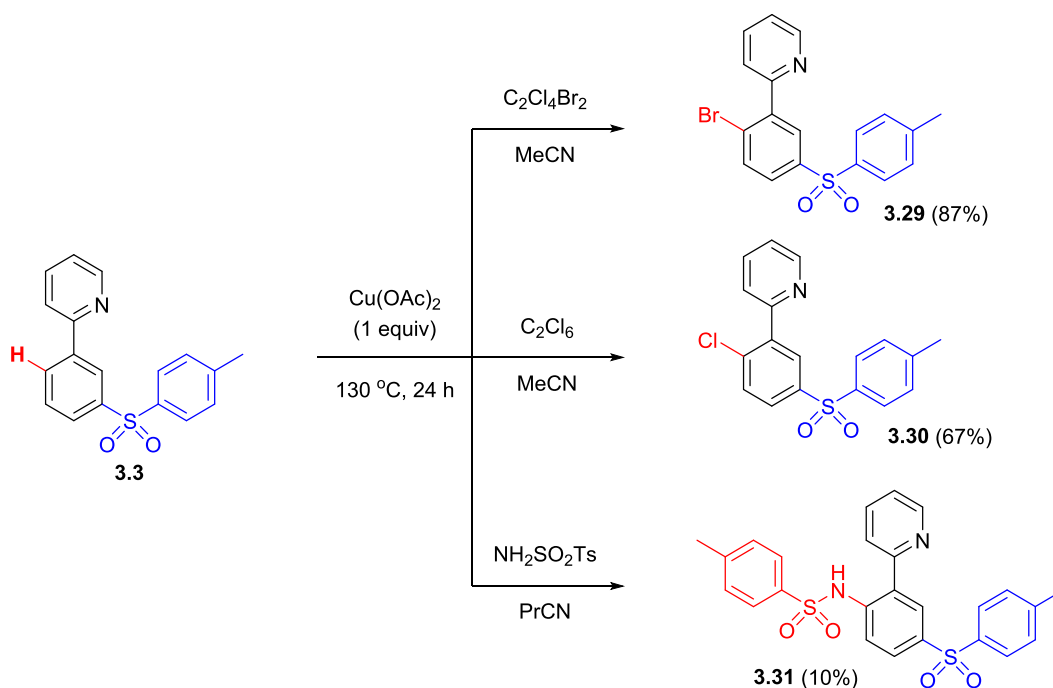
**Scheme 3.7** *meta*-sulfonated 2-phenylpyridine derivatives synthesised for reaction pathway 2

### 3.3.2 *ortho* C-H functionalisation

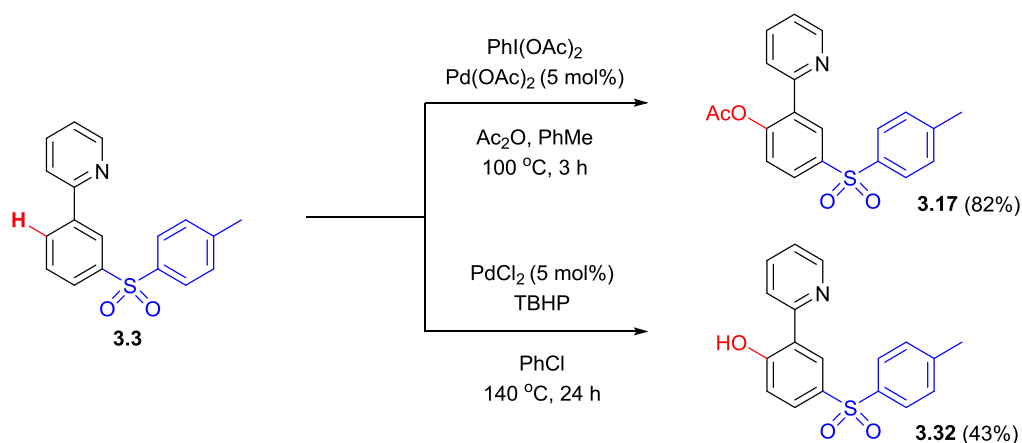
In contrast to reaction pathway 1, pathway 2 proved to be far more advantageous, both in scope and selectivity. Utilising the *meta*-sulfones synthesised previously, a range of functional groups were able to be installed in the *ortho* position in good yield. This included halogens, protected and unprotected alcohols and a sulfonamide, as well as intentional oxidative homocoupling to form dimeric species. The most important observation from reaction pathway 2 is the complete regioselectivity it gave for the C8-C11 substituted isomers, with no other byproducts being formed.

Bromination was achieved using the same methodology demonstrated to work on 2-phenylpyridines in reaction pathway 1, with the modified bromine source, furnishing brominated analogue **3.29** in excellent yield. Chlorinated analogue **3.30** was obtained in a



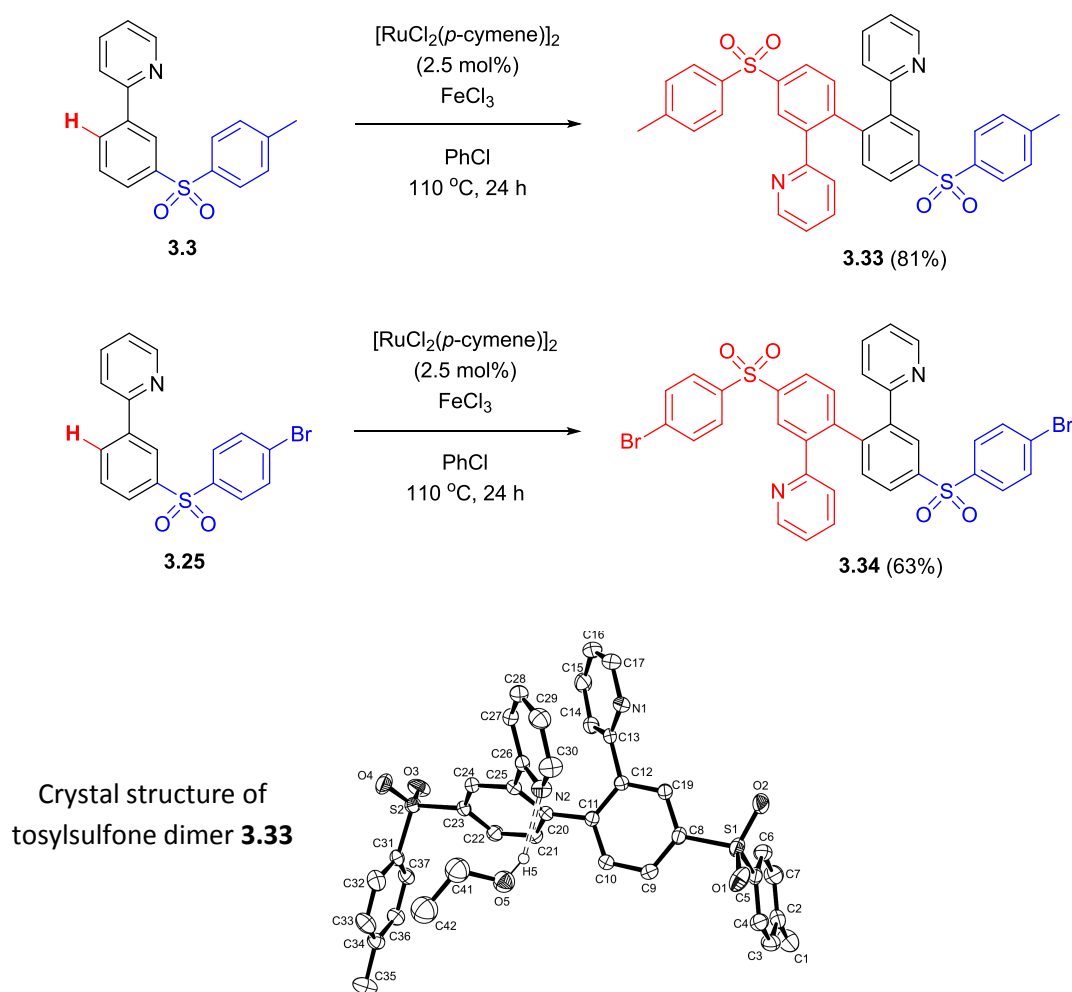


**Scheme 3.8** Cu-catalysed *ortho* functionalisation of *meta*-sulfonated 2-phenylpyridines



**Scheme 3.9** Pd-catalysed *ortho* functionalisation of *meta*-sulfonated 2-phenylpyridines

similar fashion. It was found that by switching the halogen source from  $\text{C}_2\text{Cl}_4\text{Br}_2$  to  $\text{C}_2\text{Cl}_6$ , the same Cu-catalysed protocol could also be used to affect chlorination in good yield, albeit notably lower than in the case of bromination. A small amount of sulfonamide **3.31** was obtained by replacing the halogen source with *p*-toluenesulfonamide and opting for the higher boiling solvent butyronitrile. Along with these Cu-mediated examples, the two Pd-catalysed functionalisations used in pathway 1 were used to install OH and OAc substituents. Acetoxylation proceeded in excellent yield with only the monosubstituted



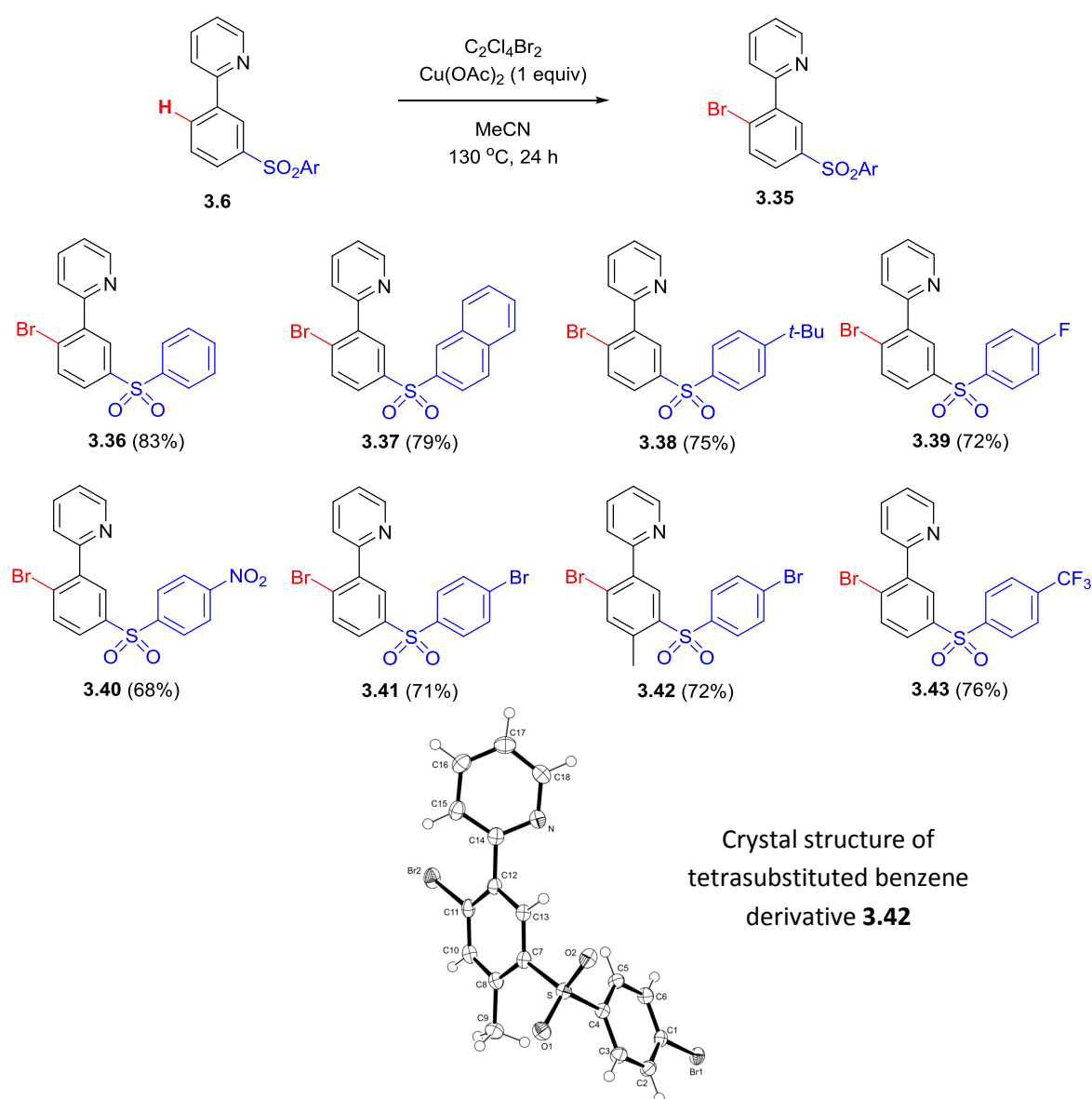
**Scheme 3.10** Ru-catalysed oxidative homocoupling of *meta*-sulfonated 2-phenylpyridines

product **3.17** obtained. This particular example serves to highlight the superiority of the *meta* then *ortho* functionalisation sequence showcased in reaction pathway 2, with its far better product yield and selectivity compared to the *ortho* then *meta* functionalisation sequence for the same compound. The *ortho* hydroxylation product **3.32** was furnished in moderate yield using  $\text{PdCl}_2/\text{TBHP}$ , again with complete selectivity.

Following on from the discovery of the dimeric byproducts in the *meta* sulfonation protocol discussed in Chapter 2, controlled oxidative homocoupling of the *meta*-sulfones was investigated as a way of accessing novel dimeric species. This was achieved using a Ru-catalysed *ortho* functionalisation methodology developed by Li.<sup>74</sup> Two *meta*-sulfonated 2-phenylpyridine dimers were obtained in good yield, with dibrominated analogue **3.34** possessing the possibility for further functionalisation (Scheme 3.10).

### 3.3.3 Bromination substrate scope

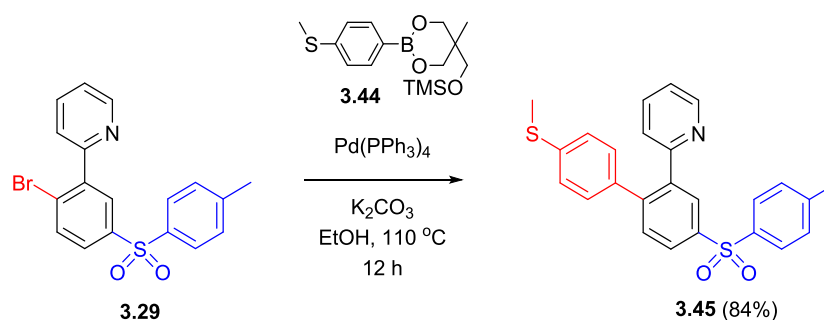
As the *ortho* bromination product **3.29** was furnished in good yield and holds the potential for further functionalisation, the scope of the bromination reaction as part of the sequential process was then explored with a range of substituted sulfones. Scheme 3.11 shows the scope of this two step protocol. In general, electron withdrawing groups afforded the highest yields, with some weakly donating groups being tolerated. Additional electron-donating functionality on the aromatic ring allowed the selective synthesis of the tetrasubstituted benzene derivative **3.42** in good yield.



**Scheme 3.11** Scope of sequential *meta* C-S and *ortho* C-Br bond formation.

### 3.3.4 Further functionalisation

The brominated products from sequential C-H functionalisation protocol could be further elaborated, as shown by the Suzuki coupling of **3.29** with dioxaborinane **3.44** (for further discussion on the preparation and use of dioxaborinanes see Chapter 4, Section 4.2.1), to afford polyaryl derivative **3.45** (Scheme 3.12).



**Scheme 3.12** Product modification via Suzuki coupling

## 3.4 Conclusions

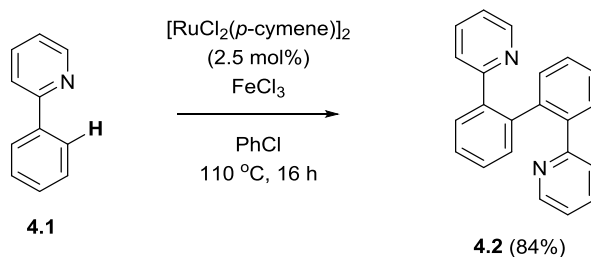
In conclusion the use of the Ru-catalysed *meta* sulfonation protocol, as part of a sequential C-H functionalisation strategy, provides access to a range of novel, highly substituted, 2-phenylpyridine derivatives. A reaction protocol for sequential chelation-assisted aromatic C-H functionalisation has been demonstrated, via a catalytic *meta*-directed C-S bond formation followed by an *ortho*-directed C-C or C-X bond forming process to give complete control over the reaction products, which were obtained in good yield and high regioselectivity. The *ortho* bromination methodology was found to be compatible with a range of functionalised sulfones and, although direct C-H arylation or alkenylation was not achieved as part of the sequential strategy, the ability to further functionalisation these brominated analogues goes some way to alleviating this issue.

## 4. Synthesis and Properties of Novel 2-Arylpyridine Dimers

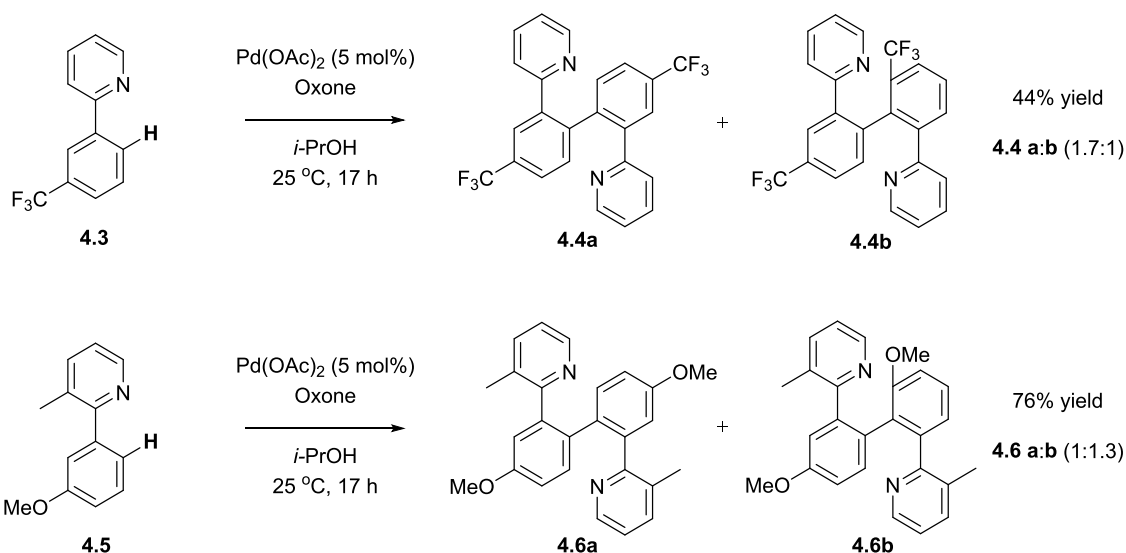
In light of the observed formation of dimeric 2-phenylpyridine species as byproducts from the Ru-catalysed *meta* sulfonation protocol, disclosed in Chapter 2, it was felt that further investigation into their synthesis and properties could be beneficial to ongoing work on regioselective C-H functionalisation. At this point the hypothesis that they could be acting as bidentate ligands for Ru, and so forming an active catalytic species in situ, had been somewhat discredited, however this could not be proven conclusively until attempts had been made to isolate transition metal complexes of these dimeric species. This chapter deals with the synthesis, characterisation and properties of novel 2-arylpyridine dimers and exploration of their potential to act as bidentate ligands.

### 4.1 Chelation-assisted Oxidative Homocoupling

There are several catalyst systems utilising different transition metals that have been developed for the homocoupling of 2-arylpyridines. Li observed the formation of small quantities of 2-arylpyridine dimers as by-products in the cross-dehydrogenative coupling of 2-phenylpyridine derivatives with cycloalkanes, in the presence of  $[\text{RuCl}_2(p\text{-cymene})]_2$  and TBHP as terminal oxidant.<sup>75</sup> Upon re-optimisation of the reaction conditions to favour formation of the dimers, it was found that replacing TBHP with  $\text{FeCl}_3$  afforded excellent yields.<sup>74</sup> The authors also noted that it was actually beneficial to decrease the amount of oxidant used to 0.8 equivalents, to prevent coordination of  $\text{FeCl}_3$  to the nitrogen in the pyridine ring and hinder cyclometalation. Substituents in the 3- and 4- positions on the phenyl ring proceeded readily, but substituents in the 6- position significantly lowered yields, even with increased reaction times (Scheme 4.1).

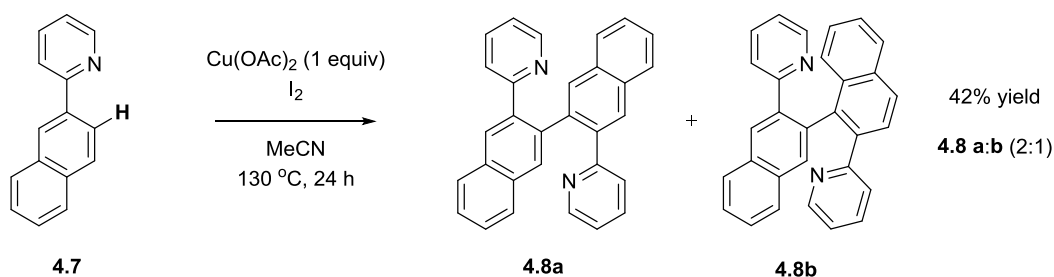


**Scheme 4.1** Ru catalysed homocoupling of 2-phenylpyridines



**Scheme 4.2** Pd catalysed dimerisation of 2-phenylpyridines

Sanford reported a  $\text{Pd}(\text{OAc})_2$  catalysed system at mild temperatures, using Oxone to regenerate the active species.<sup>76</sup> In contrast the ruthenium-catalysed protocol, this methodology gave good to excellent yields for several substituents at the 6- position on the phenyl ring with 100% selectivity (Scheme 4.2). However, when substituents were introduced at the 4-position two regioisomers were obtained. Where the *meta*-substituent was electron donating, the unsymmetrical product **4.6b** was slightly favoured, while an electron-withdrawing substituent showed a preference for the symmetrical product **4.4a**. The same authors have also illustrated the synthesis of 2-phenylpyridine dimers from pre-prepared Ni and Pd complexes.<sup>77, 78</sup> A copper mediated procedure for pyridine-directed homocoupling was outlined by Yu, again stemming from byproducts found in previous work.<sup>79</sup> The use of stoichiometric quantities of  $\text{Cu}(\text{OAc})_2$  and iodine in acetonitrile were found to furnish dimers with a variety of substituents in moderate yields. They propose an initial in situ iodination followed by Ullmann type coupling for the formation of the dimeric species, also noting the choice of solvent to be critical as the use of dichloroethane (DCE) stopped the reaction after iodination and did not promote Ullmann coupling. The vast majority of substrates showed complete regioselectivity, with the exception of the naphthyl derivative **4.7** which formed a mixture of regioisomers **4.8a** and **4.8b** in a ratio of 2:1, favouring the less sterically hindered adduct (Scheme 4.3).



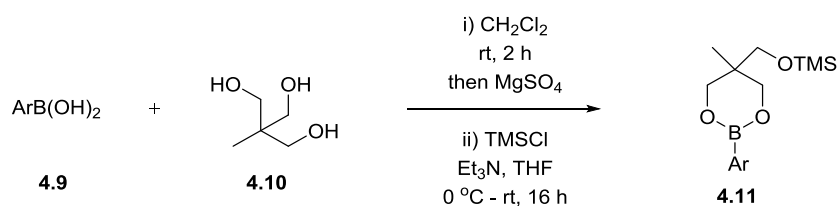
**Scheme 4.3** Cu-mediated homocoupling of 2-(naphthyl)pyridine

## 4.2 Synthesis of 2-arylpyridines via Suzuki Coupling

In order to facilitate expedient synthesis of a range of potentially interesting dimeric species, a sequential synthetic strategy was devised composing of Suzuki coupling of the required aryl motif with 2-bromopyridine to yield the monomer, followed by Ru-catalysed oxidative homocoupling to form the dimer.

### 4.2.1 Dioxaborinanes

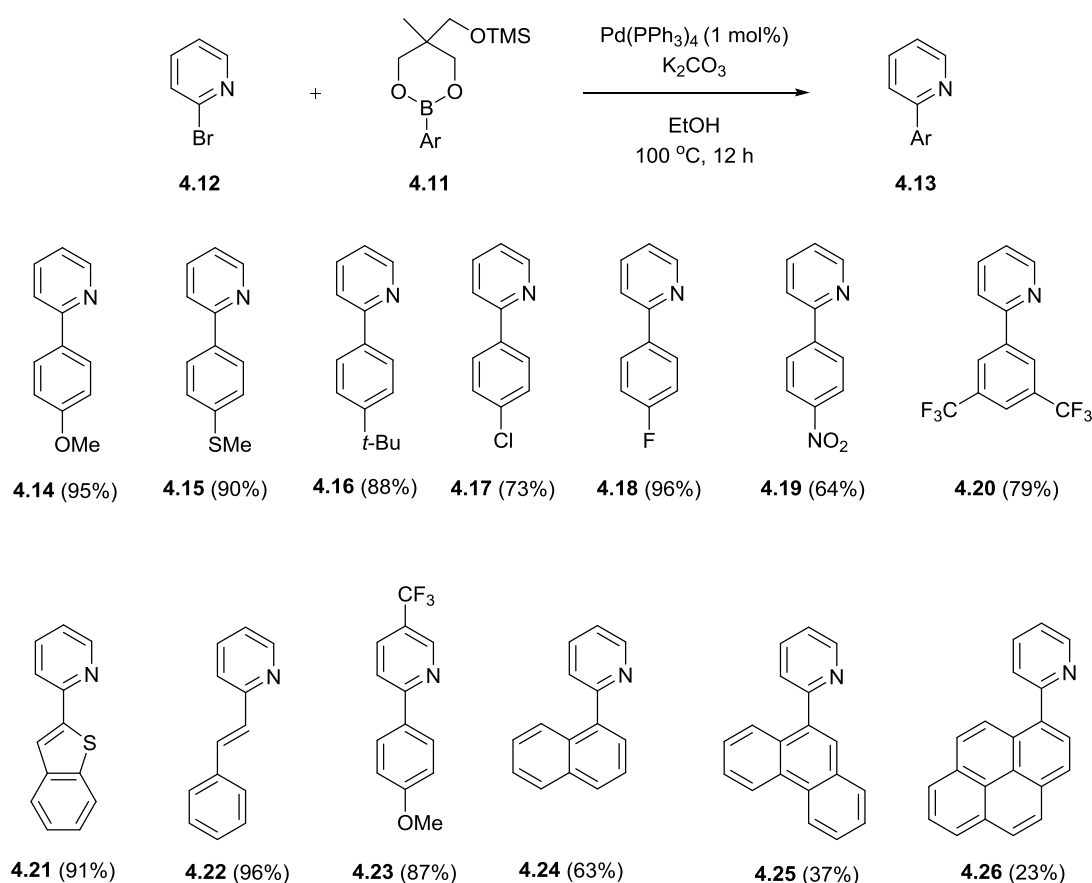
A novel class of boron reagent has been developed within the Frost group for use in Rh-catalysed conjugate addition reactions.<sup>80, 81</sup> Recently, their use has been extended to Suzuki couplings, where it has shown significant advantages over boronic acids and some other more conventional boron reagents such as MIDA boronates and  $\text{BF}_3\text{K}$  salts. These dioxaborinanes (**4.11**) are facile to prepare have been shown to be superior to boronic acids in the synthesis of challenging 2-arylpyridines via Suzuki coupling.<sup>82</sup> For this reason they were the reagent of choice for the first step in the sequence. All of the required dioxaborinanes were already available in-house and used without further modification.



**Scheme 4.4** Dioxaborinane synthesis from boronic acids

### 4.2.2 Suzuki coupling

A variety of 2-arylpyridines were synthesized from the corresponding dioxaborinane via Suzuki coupling with 2-bromopyridine **4.12**, using  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{K}_2\text{CO}_3$  in EtOH at 100 °C. In the majority of cases these conditions gave good to excellent yields of the required 2-arylpyridine derivatives in a reaction time of 12 h (Scheme 4.2). The exceptions to this being **4.25** and **4.26**, with these extended aromatic systems being much less reactive towards coupling, however the yields were still consistent with the literature.<sup>82</sup> The substrates were chosen in order to explore the, so far limited, scope for the oxidative homocoupling of 2-phenylpyridine derivatives, including electron donating and withdrawing substituents as well as more interesting aromatic and heteroaromatic motifs and to see whether this methodology could potentially be extended for use with alkenes.



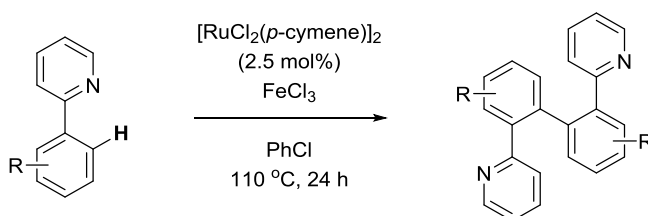
**Scheme 4.5** Range of 2-arylpyridines synthesised via Suzuki coupling



### 4.3 Oxidative Homocoupling of 2-arylpyridines

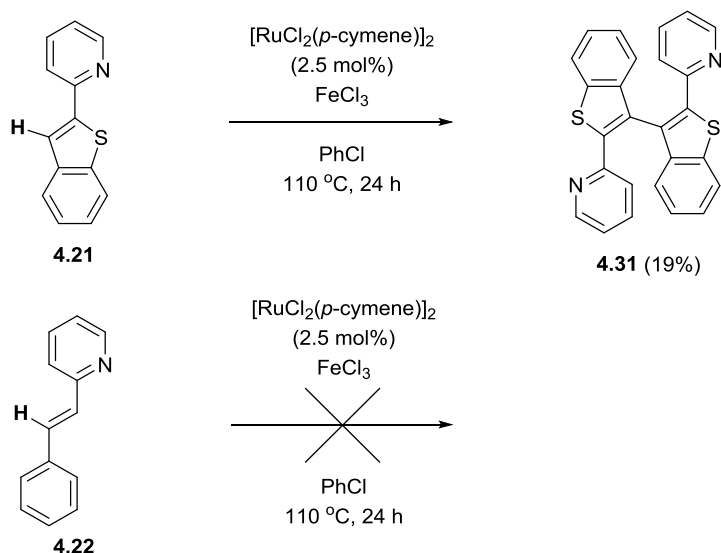
With the 2-arylpyridine derivatives in hand, they were then subjected to oxidative homocoupling using the conditions developed by Li,<sup>74</sup> employing a  $[\text{RuCl}_2(p\text{-cymene})]_2$  catalyst, with  $\text{FeCl}_3$  as terminal oxidant, in chlorobenzene at 110 °C for 24 h. Table 4.1 shows the isolated yields obtained for substituted 2-phenylpyridine derivatives with differing electronic properties. It can be seen that the substrates with electron rich and electron neutral character gave the best yields, with the exception of **4.28** which was an anomalous result with a substantially lower yield. However substitutes with even small amounts of electron withdrawing character performed badly across the board. Again the 4-Cl analogue **4.17** proved to be somewhat of an anomaly as it is only slightly less electron deficient than the 4-F example **4.18** and would be expected to give a comparable yield. A particularly ambitious target was chosen in the form of the 3,5-bistrifluoromethyl analogue **4.20** which possesses significantly more steric hindrance than other examples, as shown by its lack of reactivity with only starting material being returned.

**Table 4.1** Yield of substituted 2-phenylpyridine dimers



| Entry | Compound Number | R                   | Yield (%) |
|-------|-----------------|---------------------|-----------|
| 1     | <b>4.2</b>      | H                   | 80        |
| 2     | <b>4.27</b>     | 4-OMe               | 60        |
| 3     | <b>4.28</b>     | 4-SMe               | 27        |
| 4     | <b>4.29</b>     | 4- <i>t</i> -Bu     | 84        |
| 5     | -               | 4-Cl                | 0         |
| 6     | <b>4.30</b>     | 4-F                 | 21        |
| 7     | -               | 4-NO <sub>2</sub>   | 0         |
| 8     | -               | 3,5-CF <sub>3</sub> | 0         |

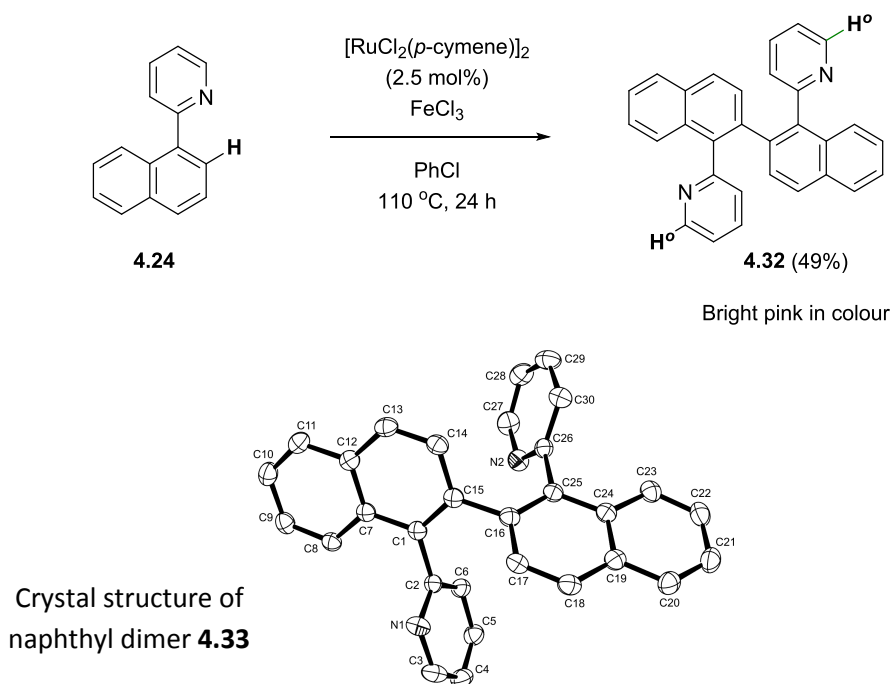
Other potentially interesting, yet challenging examples were exhibited in the form of **4.21** and **4.22**. While **4.21** proceeded to furnish the heteroaromatic dimeric species **4.31** in low yield, unfortunately no homocoupling of stilbene derivative **4.22** was observed with only starting material returned, which is perhaps not surprising considering the difference in electronic character of alkenyl  $sp^2$  C-H bonds in comparison with aryl  $sp^2$  C-H bonds.



**Scheme 4.6** Homocoupling of heteroaryl and alkyl pyridines

#### 4.3.1 Characterisation of 2-(naphthalen-1-yl)pyridine dimer

Perhaps the most intriguing result from this study was the formation of **4.32** (Scheme 4.7). In contrast to the naphthalen-2-yl variant **4.8** synthesised by Yu as a mixture of symmetrical and unsymmetrical isomers (see section 4.1), homocoupling of 2-(naphthalen-1-yl)pyridine **4.24** proceeded to furnish the corresponding dimer in a moderate 49% yield, with complete selectivity for the symmetrical isomer **4.32**, as a bright pink solid. While the observed colour was not significant in itself, within the context of this work it was the only compound to show any colour of such intensity, the other colours observed being dull browns, greens and greys if any at all, which is not unusual for reactions conducted with transition metals. The second significant observation came upon analysis of the isolated product via NMR spectroscopy. In the  $^1H$  spectrum the signal at 8.66 ppm, indicative of the proton *ortho* to nitrogen on the pyridine ring (labelled as  $H^o$  in Scheme 4.4), presented as a broad singlet in comparison to the majority of the other examples where

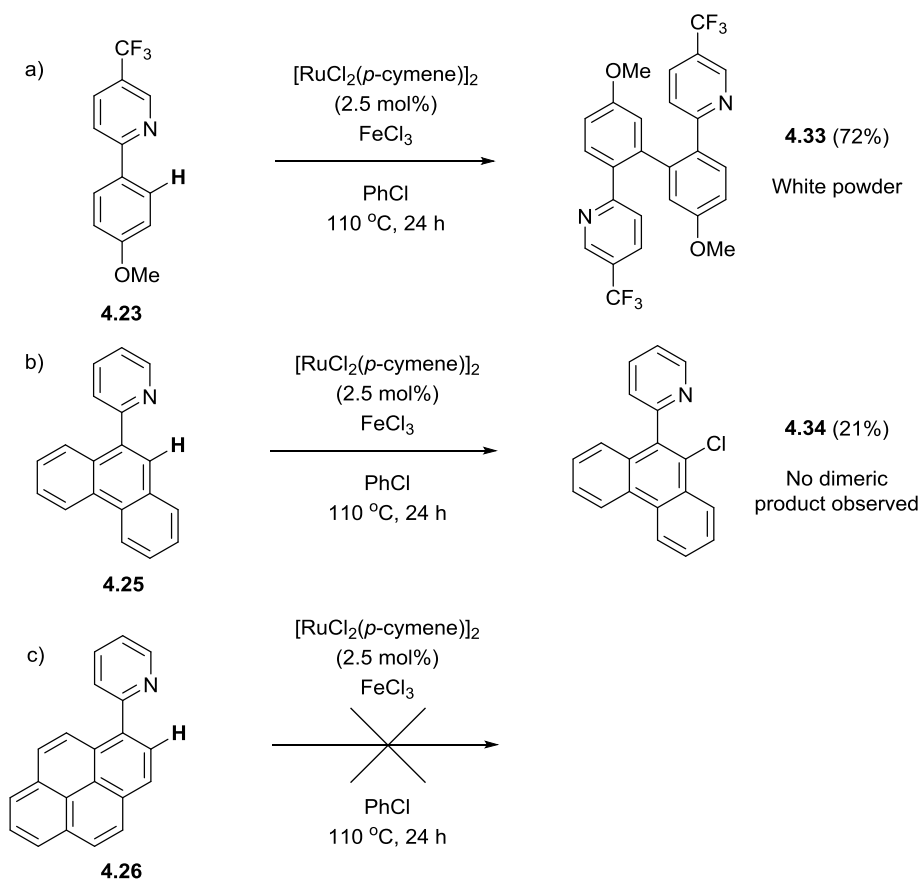


**Scheme 4.7** Homocoupling of 2-(naphthalen-1-yl)pyridine

it presents as a well defined doublet (d) or, in some cases, as a doublet of doublet of doublets (ddd). In addition, several of the quaternary peaks in the  $^{13}\text{C}$  NMR spectrum at 149.1, 135.9 and 129.2 ppm were also broader than usual. Both of these observations are usually attributed to a mixture of diastereoisomers being present.

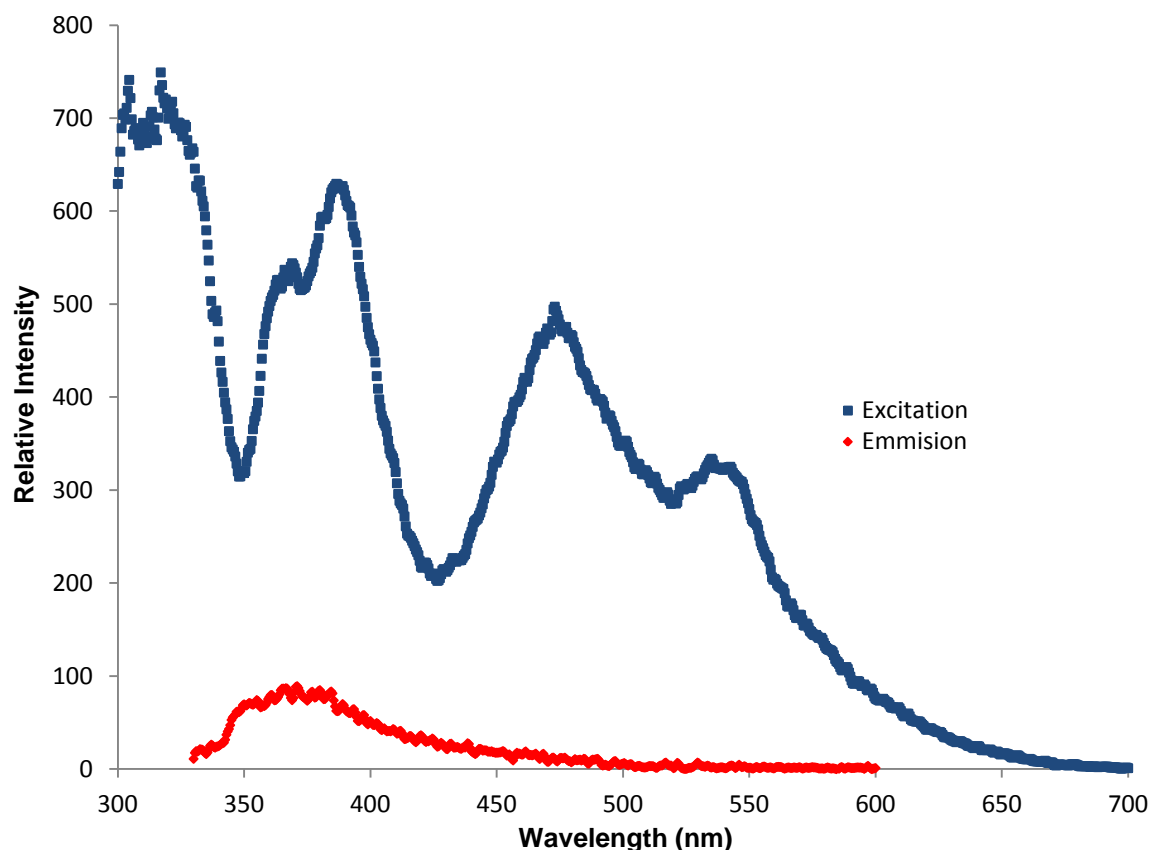
#### 4.3.1.1 Colour generation

There are two possible mechanisms that could be invoked to explain the colour generation in **4.32**. It could either be due to an intramolecular ‘push-pull’ of electrons, with the naphthalene unit acting as the electron donor and the pyridyl nitrogen as the electron acceptor, or else facilitated by intermolecular  $\pi$ - $\pi$  stacking interactions between the naphthalene units enabling the conduction of electrons throughout the extended  $\pi$  system. In an effort to determine which of these models was occurring in this case the synthesis of several similar dimeric 2-arylpyridine compounds was attempted to see if this characteristic of intense colour was also present.



**Scheme 4.8** Synthesis of additional, potentially coloured, 2-arylpyridine dimers

Dimer **4.33** possesses substituents with better electron donating (OMe) and electron accepting (3-CF<sub>3</sub>Py) capacities than those in the naphthyl derivative **4.32** and was successfully synthesised from its monomeric precursor in 72% yield. If the colour generation was a result of an intramolecular ‘push-pull’ effect then **4.33** should also exhibit colour. However, this was obtained as a white powder, with no hint of colour whatsoever. If the colour was the result of intermolecular  $\pi$ - $\pi$  stacking interactions, then dimers derived from polyaromatic 2-arylpyridines **4.25** and **4.26** should also exhibit this phenomenon, as their larger aromatic motifs will facilitate stacking more readily. Unfortunately, when subjected to oxidative homocoupling conditions, both of these compounds failed to afford any dimeric products. Phenanthrene analogue **4.25** only gave the *ortho*-chlorinated product **4.34**, while pyrene analogue **4.26** proved unreactive and only starting material was returned. This is perhaps not surprising as their extended aromatic structures will delocalise the electrons over a greater area and could make C-H



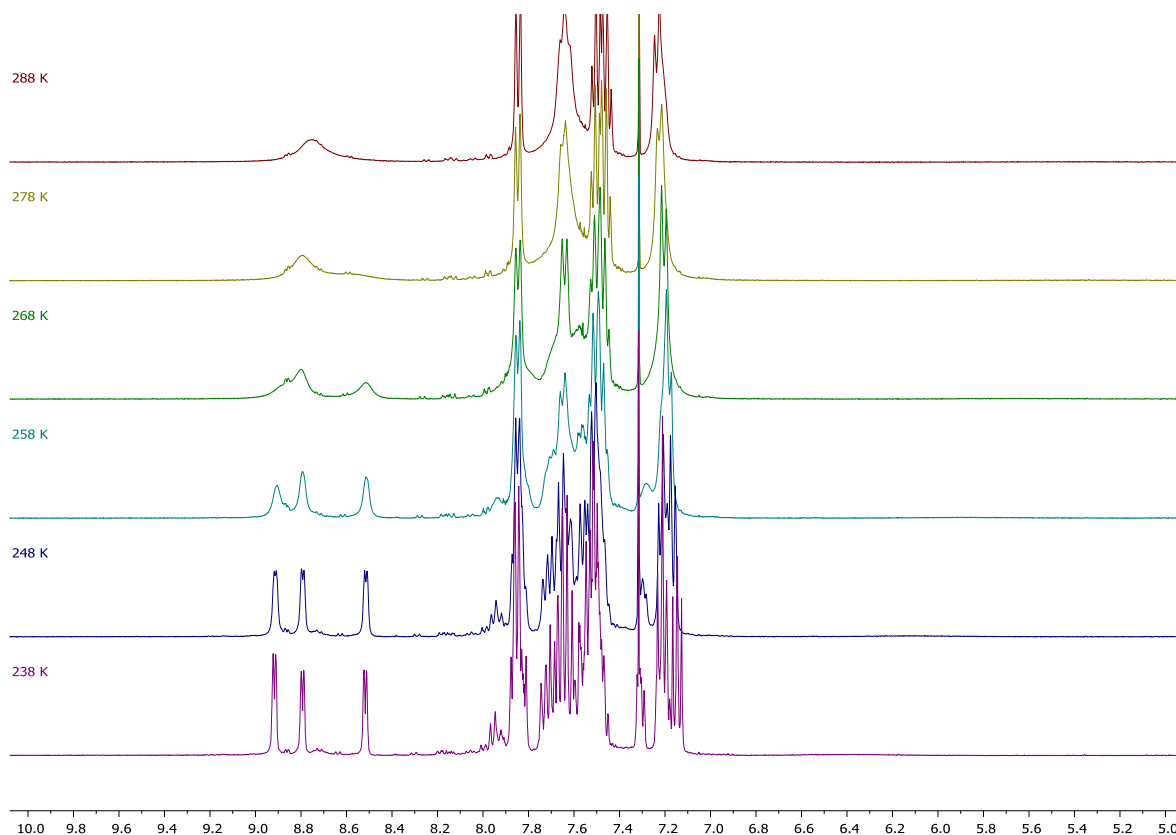
**Figure 4.1** Graph of electromagnetic excitation and emission spectrum of **4.32** in MeOH

functionalisation more difficult. Phenanthrene analogue **4.25** also has a substituent adjacent to the C-H bond undergoing functionalisation, and as seen in Chapter 3 this would be expected to impair its reactivity. These results point towards the presence of intermolecular  $\pi$ - $\pi$  stacking interactions as the origin of the colour exhibited by **4.32**, however as other examples of dimers with these properties could not be successfully synthesised, this cannot be proven conclusively.

Fluorescence studies of **4.32** in methanol showed a broad absorption band with maxima in the visible region at 389 nm and 473 nm (Figure 4.1). This observation of absorbance of a broad range of wavelengths, with maxima in the blue and green regions of the visible spectrum, is consistent with the observed pink colour. Upon measurement of the emission spectrum of **4.32** at an excitation wavelength of 330 nm, an emission peak at 352 nm was observed, but only with a fraction of the intensity of the absorbance. While this shows that **4.32** is indeed fluorescent, it is not very efficient and the majority of electrons in the excited state are quenched by competing photochemical processes.

#### 4.3.1.2 Variable temperature $^1\text{H}$ NMR spectroscopic studies

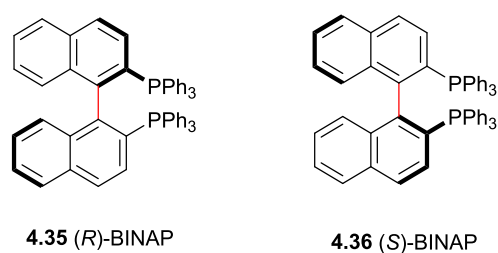
Uncharacteristically broad peaks in a  $^1\text{H}$  NMR spectrum, such as the signal seen at 8.66 ppm in the spectrum of **4.32**, are usually attributed to the presence of a mixture of diastereoisomers, which was unexpected in this case as it had not been seen with any of the other substrates. To investigate this further a variable temperature  $^1\text{H}$  NMR spectroscopic study was conducted, in which  $^1\text{H}$  NMR spectra were taken at different temperatures between 288 and 238 K, in decreasing increments of 10 K. It was thought that lowering the temperature would allow for better resolution of the broad signal and be able to determine if **4.32** was present as more than one isomer. The results of the study are shown in Figure 4.2. It can be seen that, with each incremental decrease in temperature, the broad singlet is gradually resolved into three separate doublet peaks at 8.92, 8.78 and 8.52 ppm respectively. This suggests the presence of at least two magnetically inequivalent protons in the molecule. However, they could not be diastereotopic as there was no possibility of forming any stereogenic centres during the reaction.



**Figure 4.2** Variable temperature  $^1\text{H}$  NMR spectra of **4.32** between 288 and 238 K

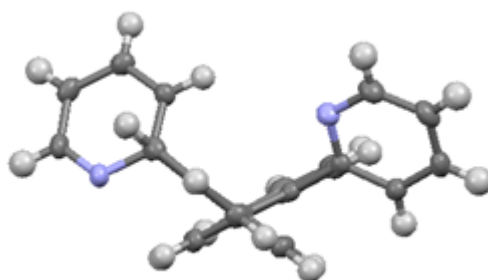
#### 4.3.1.3 Atropisomerism

In an effort to rationalise these findings, it was proposed that **4.32** could be displaying atropisomerism. Atropisomers do not contain any stereogenic centres, but still possess axial chirality due to the restricted rotation of substituents around a single bond.<sup>83</sup> A common example of this is displayed in the chiral ligand BINAP, where the sterically bulky phosphines and adjacent naphthalene protons prevent free rotation around the biaryl bond (shown in red in Scheme 4.6) and give rise to two unsymmetrical isomers (*R*)-BINAP **4.35** and (*S*)-BINAP **4.36**.

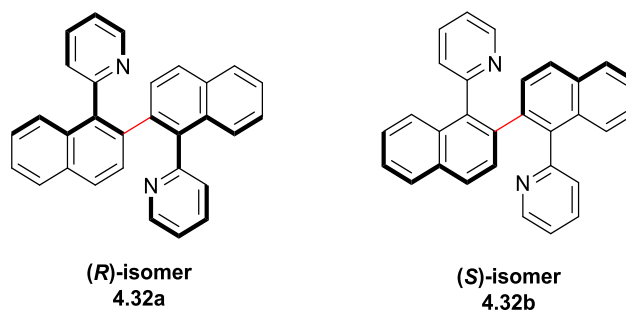


**Scheme 4.9** BINAP chirality imparted by restricted rotation around the biaryl bond

Although the naphthalene units in **4.32** are bonded at C2, as opposed to C1 in BINAP, it is still conceivable that rotation around the newly-formed *ortho* C-C bond at C2 could also be restricted and thus explain the presence of axial chirality. Moreover, when the crystal structure of **4.32** was viewed along the axis of this bond, the naphthalene units could be seen to be perpendicular to one another (Figure 4.3), as is the case with BINAP.



**Figure 4.3** Crystal structure of **4.32** viewed along the binaphthyl bond



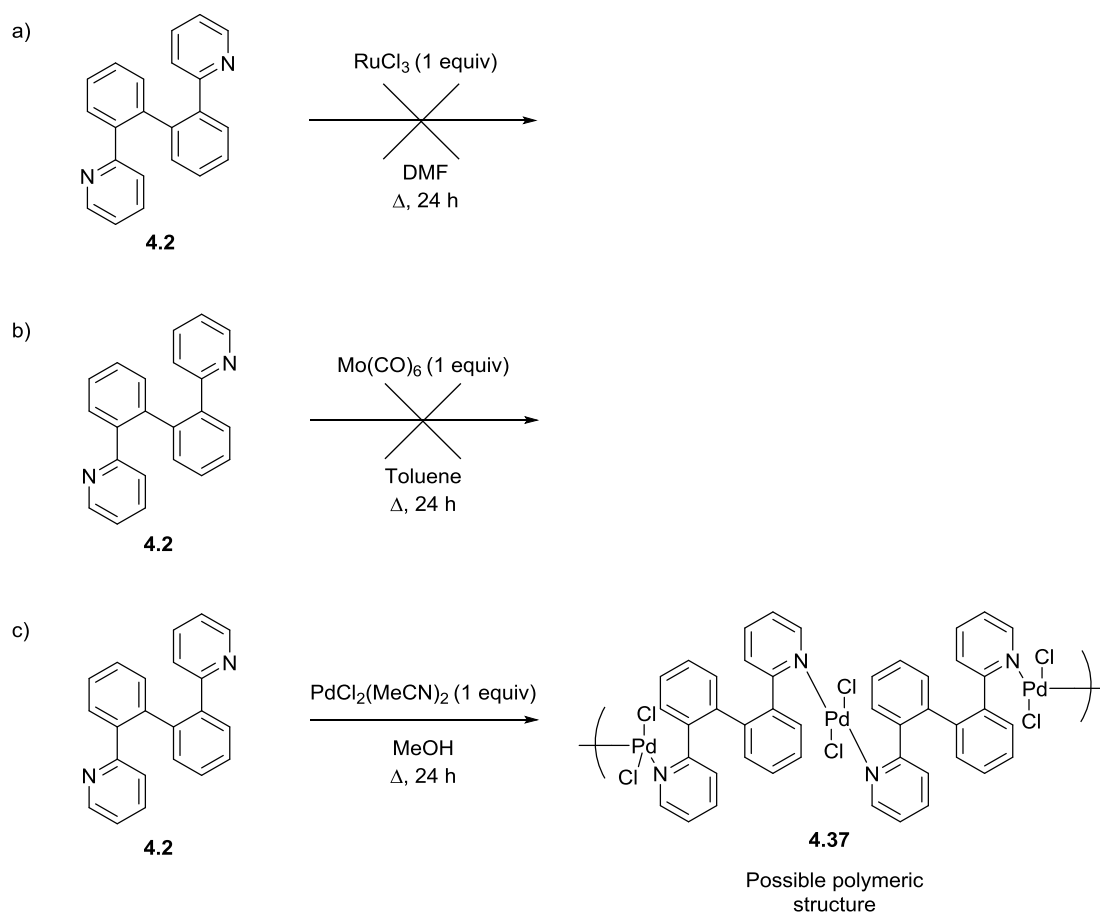
**Scheme 4.10** (R)- and (S)-isomers of 2-(naphthalen-1-yl)pyridine

Using Cahn-Ingold-Prelog priority rules, the crystal structure is found to be the (*R*)-isomer **4.32a** however, the (*S*)-isomer will also be present and when in solution an equilibrium would exist between the (*R*)- and (*S*)-isomers, culminating in the broad signals observed in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. But this alone is not enough to account for the presence of the three well defined peaks, as seen in the  $^1\text{H}$  NMR run at 238 K. This could possibly arise from additional restricted rotation of the pyridyl-naphthyl C-C bonds, however if this were the case then; with two atropisomers containing two of these bonds each, up to eight different proton environments could be hypothesised, which are not seen in the spectra. Chiral HPLC was used to try and resolve the atropisomers, however no separation could be obtained and it was felt that compound **4.32** did not warrant further analysis, unless a use could be found for the novel dimeric compound.

#### 4.4 Preparation of Transition Metal Complexes

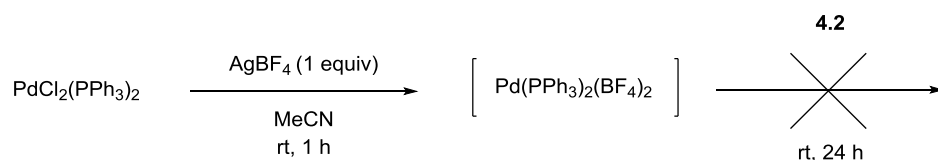
To be able to determine whether or not these 2-arylpyridine dimers could be useful as novel bidentate ligands, attempts were made to prepare transition metal complexes of the 2-phenylpyridine dimer **4.2**. As the role of **4.2** in the *meta* sulfonation protocol was of interest, the synthesis of a Ru complex was attempted using  $\text{RuCl}_3$  as the precursor, along with complexes of Pd (from  $\text{PdCl}_2(\text{MeCN})_2$ ) and Mo (from  $\text{Mo}(\text{CO})_6$ ). Although Cu was perhaps an obvious choice it was felt that, due to the size of the dimer, it would be likely to form a tetrahedral Cu(II) complex, which would be paramagnetic and difficult to characterise, so Cu was left out.





**Scheme 4.11** Attempted synthesis of transition metal complexes

The reactions using ruthenium (Scheme 4.11a) and molybdenum (Scheme 4.11b) were unsuccessful and did not afford any of the corresponding dimer complexes. However, the reaction in which  $\text{PdCl}_2(\text{MeCN})_2$  was used as the precursor formed a white precipitate. The precipitate was collected by gravity filtration as a powdered solid and attempts were made to grow crystals of it and analyse them by X-ray crystallography. The solid proved to be insoluble in everything but DMSO and after repeated attempts at recrystallisation from DMSO/ $\text{H}_2\text{O}$ , no crystals could be obtained. Due to the sterically hindered nature of the 2-phenylpyridine dimer **4.2** formation of a bidentate complex would be difficult and it would be more likely to form a polymeric species, similar to **4.37**, which would explain the observed insolubility.



**Scheme 4.12** Attempted synthesis of a Pd complex with improved solubility

In an effort to shed more light on this result, an additional experiment was carried out using a different Pd precursor  $\text{PdCl}_2(\text{PPh}_3)_2$ , containing phosphane ligands, which should improve its solubility. As these ligands are not be as labile as the MeCN ligands on the first precursor,  $\text{AgBF}_4$  was used to exchange for the chlorides and produce a more reactive Pd intermediate, before introduction of **4.2**. The formation of the  $\text{Pd}(\text{PPh}_3)_2(\text{BF}_4)_2$  intermediate was confirmed by  $^{31}\text{P}$  NMR, with a shift in the triphenylphosphane peak from 34.9 to 42.9 ppm. However after addition of **4.2** no such change was observed with the peak at 42.9 ppm still present in the  $^{31}\text{P}$  NMR spectra, indicating that no complex had been formed. No further attempts were made to elucidate the structure of **4.37**.

## 4.5 Conclusions

In conclusion, a range of 2-arylpyridine dimers were synthesised as part of an effort to widen the scope of the Ru-catalysed oxidative homocoupling methodology and investigate the potential of the resulting dimeric species for use as bidentate ligands. Suzuki coupling of dioxaborinanes with 2-bromopyridine furnished the 2-arylpyridines in good yield followed by homocoupling, to give several novel 2-arylpyridine dimers. Electron rich arenes fared the best, with any sort of electron withdrawing substituent hindering the reaction significantly. The 2-naphthylpyridine dimer exhibited an interesting case of atropisomerism, which was characterised using variable temperature  $^1\text{H}$  NMR spectroscopy and X-ray crystallography and also was found to be highly coloured, which is believed to be the result of intermolecular  $\pi$ - $\pi$  stacking interactions. Attempts to synthesise transition metal complexes of these dimers was largely unsuccessful, with the exception of a Pd complex which was thought to be polymeric, although this could not be conclusively proven due to its poor solubility.

## 5. Coupling Reactions in Continuous-Flow Systems

### 5.1 Introduction

Continuous flow processing has received a significant amount of interest from both academia and industry over the last decade for application in organic synthesis.<sup>13, 88-91</sup> This is in part due to the economic and resource efficiencies demonstrated by the bulk and petrochemical sectors of the chemical industry,<sup>92</sup> which both operate the majority of processes on a continuous flow basis. It is now increasingly seen as desirable to adapt continuous flow methodologies for the predominantly synthetic, high value, low volume end of the market, within which palladium catalysed cross-couplings play a significant role.<sup>93, 94</sup>

Continuous flow processing is part of a group of so-called 'enabling technologies for organic synthesis'<sup>95</sup> designed to improve the speed, efficiency, separation and scalability of chemical transformations and when used in conjunction with other enabling technologies such as supported catalysts,<sup>96</sup> alternative (non-classical) solvents<sup>97-99</sup> and microwave irradiation<sup>100</sup> can provide unique advantages and opportunities for synthetic and process chemists alike. Greater reaction efficiencies can be achieved through the ability to operate with reduced solvent volumes, improving mass transfer and reducing reagent stoichiometry. In terms of energy use, the ability to operate with static mixers, negating the need for additional agitation and the significantly reduced volumes of material that require heating or cooling, both make continuous processing more energy efficient than batch. The significantly smaller reaction volumes also provide better reaction control and ensure consistency in the quality of the products. By maintaining uniformity throughout the reaction environment and allowing precise temperature control, continuous flow can lead to higher conversions/selectivities and prevent runaway reaction exotherms. Separation processes in continuous flow systems can be significantly easier than in batch operations, with the use of scavenger columns and in-line continuous extraction, as well as with the aid of supported catalysts and reagents, which can be incorporated into packed columns that are simple to wash or replace and negate the need for filtration. Scaling-up flow systems is substantially easier than batch based processes because the reaction environments can be kept almost identical to that on a lab scale.<sup>101</sup> This can be achieved by either increasing the running time of the reactor

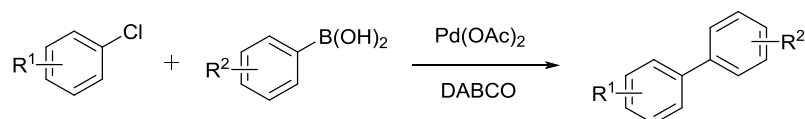
(scaling up) or by running numerous reactors simultaneously (numbering up),<sup>102</sup> thereby increasing throughput. Effectively this leads to reaction miniaturisation and incorporates the philosophy of process intensification, as well as reducing the financial burden associated with scaling up a process.

All of these advantages are making continuous flow systems an attractive alternative to batch processing for modern organic synthesis. Among the numerous examples of catalysis that have been conducted in flow, palladium catalysed cross-couplings are one of the most widely studied (for recent reviews see Buchwald<sup>88</sup> and Frost<sup>96</sup>). This chapter introduces the concept of continuous flow processing as a tool to extend the scope of cross couplings, through the possibility of using more extreme conditions to access new products, in addition to the subsequently alluded to potential for improving efficiency, reducing waste and making coupling reactions more accessible for large scale, high value applications.

## 5.2 Coupling Reactions in Flow

### 5.2.1 Suzuki-Miyaura coupling

Suzuki couplings have become a routine transformation in synthetic chemistry and as such there has been much interest in translating their use into continuous flow processing. A demonstration of the efficiency of flow vs batch for Suzuki couplings was undertaken by Li and co-workers.<sup>103</sup> They reported Suzuki coupling of both electron-rich and electron-poor aryl chlorides with phenyl boronic acid, catalyzed by a non-phosphane ligand catalyst system Pd(OAc)<sub>2</sub>/DABCO, in a capillary microreactor at 50 °C (Table 5.1). Quantitative yields were obtained for most substrates with a relatively long residence time of four hours. However, conversions of only 12-69% were achieved under the corresponding batch conditions, which required 24 h to achieve full conversion. The drive for achieving low catalyst loadings and high turnover frequencies (TOF) is as prevalent in continuous processing as it is in batch. The lowest catalyst loading reported to date using a flow protocol is 0.05 mol%.<sup>104</sup> Noel and Musacchio have reported the Suzuki coupling of heteroaryl halides with aryl and heteroarylboronic acids, using X-Phos Pd precatalyst **5.1** (0.05-1.5 mol%) and phase transfer catalyst (TBAB) in the presence of aq. K<sub>3</sub>PO<sub>4</sub>, as shown in Table 5.2.

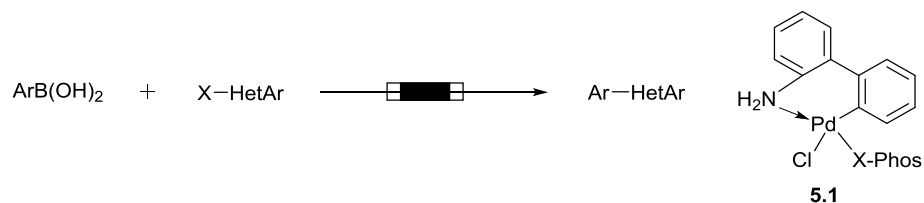
**Table 5.1** Comparison of batch vs flow for Suzuki coupling.

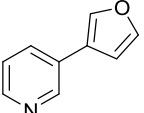
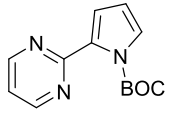
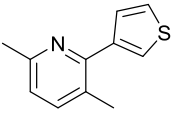
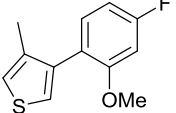
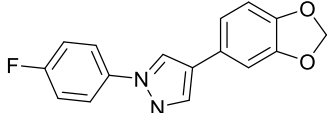
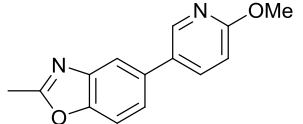
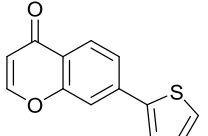
| Entry <sup>[a]</sup> | Product | Conversion (%) <sup>[b]</sup> |             |              |
|----------------------|---------|-------------------------------|-------------|--------------|
|                      |         | Flow (4 h)                    | Batch (4 h) | Batch (24 h) |
| 1                    |         | 98                            | 61          | 98           |
| 2                    |         | 99                            | 56          | 99           |
| 3                    |         | 99                            | 52          | 86           |
| 4                    |         | 99                            | 35          | 57           |
| 5                    |         | 99                            | 68          | 99           |
| 6                    |         | 99                            | 65          | 99           |
| 7                    |         | 97                            | 54          | 95           |
| 8                    |         | 99                            | 69          | 99           |

[a] Reaction conditions: aryl chloride, arylboronic acid, Pd(OAc)<sub>2</sub> (3 mol%), DABCO (6 mol%), TBAB (10 mol%), K<sub>3</sub>PO<sub>4</sub>, 50 °C. [b] Determined by <sup>1</sup>H NMR.

An efficient packed bed system was exploited to ensure good mixing of the biphasic medium consisting of NMP/toluene/H<sub>2</sub>O (4:1:5) (see Figure 5.9, section 5.3.2.2). Excellent yields were obtained at 90 °C in a residence time of 3 min, for the vast majority of heteroaryl substrates examined. Flow processing also offers advantages to high throughput synthesis and compound library preparation due to the uniformity of reaction environment and ability to be fully automated. Ley and Baxendale demonstrated the possibility of utilising microreactors for the synthesis of a library of biaryls via Suzuki coupling.<sup>105</sup> The use of Pd EnCat in conjunction with microwave irradiation provided a platform from which to screen an extensive variety of coupling partners. A total of 341

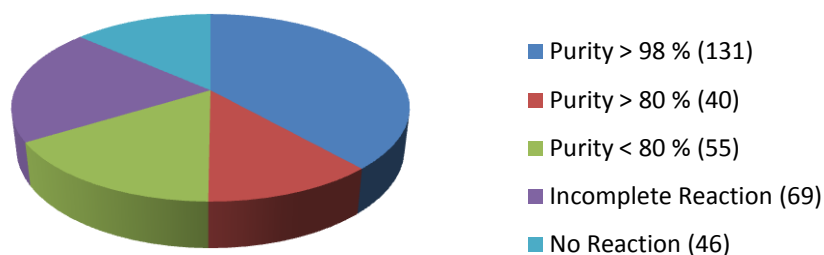
**Table 5.2** Suzuki coupling of heteroaromatics in flow.



| Entry <sup>[a]</sup> | Product   | X   | Pd (mol%) | Yield (%) |
|----------------------|---|-----|-----------|-----------|
| 1                    |    | Cl  | 1.5       | 92        |
| 2                    |    | Cl  | 1.0       | 87        |
| 3                    |    | Cl  | 0.5       | 98        |
| 4                    |   | Br  | 0.5       | 88        |
| 5                    |  | Br  | 1.5       | 89        |
| 6                    |  | Cl  | 0.5       | 96        |
| 7                    |  | OTf | 0.2       | 84        |

[a] Reaction conditions: HetArX, ArB(OH)<sub>2</sub>, X-Phos Pd precatalyst **5.1**, NMP/toluene/H<sub>2</sub>O (4:1:5), K<sub>3</sub>PO<sub>4</sub>, TBAB (10 mol%), 90 °C, 3 min residence time.

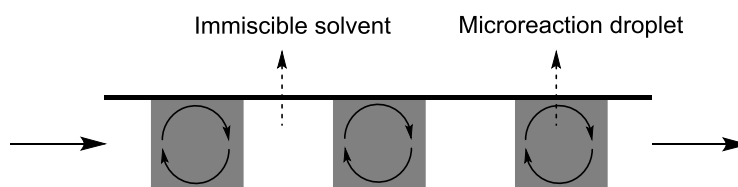
Suzuki couplings were conducted including an automated sequence of 10 in succession with short wash periods in between. Figure 5.1 shows the spread of results obtained.



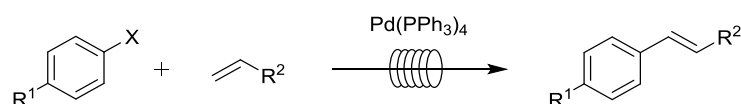
**Figure 5.1** Results of the library synthesis via continuous flow Suzuki coupling.

### 5.2.2 Mizoroki-Heck coupling

Mizoroki-Heck couplings have been developed for use in flow with a variety of different Pd catalyst systems and coupling reagents. A novel approach to achieving high conversions in flow has been devised by Wirth and co-workers who used a segmented flow technique to form micro droplet reaction environments inside the reaction channel, which gave much better yields than with laminar flow.<sup>106</sup> The optimal catalyst for this system was found to be  $\text{Pd}(\text{PPh}_3)_4$  (10 mol%), using  $\text{Et}_3\text{N}$  as the base in DMF. The segmented flow regime, shown in Figure 5.2, was formed by pumping a solution of aryl halide in DMF, a separate solution of alkene also in DMF and a third immiscible solvent perfluorodecalin, at equal flow rates into a T-mixer. The microreactor was heated to 70 °C or 130 °C, for iodides and bromides respectively to give moderate to good yields with a residence time of 40 min (Table 5.3).



**Figure 5.2** – Microreaction environments formed by segmented laminar flow.

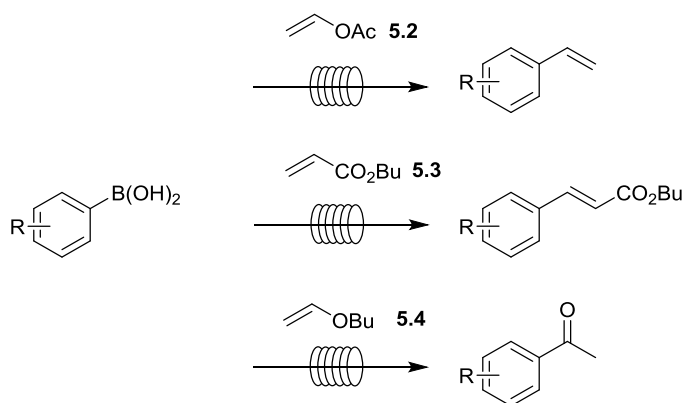
**Table 5.3** Heck coupling of aryl halides and diazonium salts in segmented flow.

| Entry <sup>[a]</sup> | R <sup>1</sup>  | R <sup>2</sup>                                | X               | Yield (%) |
|----------------------|-----------------|---|-----------------|-----------|
| 1                    | H               | CO <sub>2</sub> Me                            | I               | 68        |
| 2                    | H               | Ph  | I               | 57        |
| 3                    | H               | CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | I               | 63        |
| 4                    | Me              | CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | I               | 49        |
| 5 <sup>[c]</sup>     | NO <sub>2</sub> | Ph  | Br              | 65        |
| 6 <sup>[b]</sup>     | H               | CO <sub>2</sub> Me                            | NH <sub>2</sub> | 54        |
| 7 <sup>[b]</sup>     | H               | Ph  | NH <sub>2</sub> | 66        |
| 8 <sup>[b]</sup>     | H               | FC <sub>6</sub> H <sub>4</sub>                | NH <sub>2</sub> | 72        |
| 9 <sup>[b]</sup>     | OMe             | Ph  | NH <sub>2</sub> | 33        |
| 10 <sup>[b]</sup>    | I               | CO <sub>2</sub> Me                            | NH <sub>2</sub> | 90        |

[a] Reaction condition A: Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%), aryl halide, alkene, Et<sub>3</sub>N, DMF, 70 °C, residence time 40 min. [b] Reaction condition B: Pd(OAc)<sub>2</sub> (10 mol%), aniline derivative, alkene, *t*-BuONO, AcOH, DMF, 0-25 °C, residence time 27 min. [c] 130 °C.

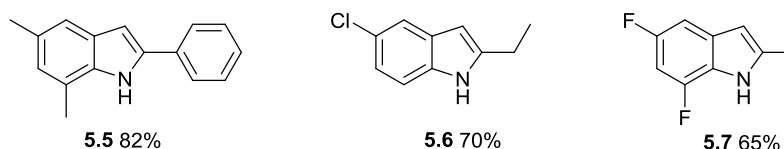
They also exploited this regime for the coupling of arenediazonium salts, generated in situ, which gave good yields with 27 min residence times. Diazonium salts rapidly decompose to form nitrogen gas and as such can be explosive and problematic for scale up. Using this continuous flow protocol, only small quantities of the diazonium salt are generated and reacted almost immediately, allowing for safe use of these hazardous reagents. Other coupling partners that have been reported in flow are arylboronic acids. Lahred et al. reported coupling of arylboronic acids with vinyl acrylate **5.2**, butyl vinyl ether **5.3** and butyl acrylate **5.4** via Heck coupling (Scheme 5.1).<sup>107</sup> Residence times of 2-5 min and temperatures of 130-150 °C gave good to excellent yields for each alkene, with Pd(OAc)<sub>2</sub> (2 mol%) and dppp (2 mol%) in DMF.





**Scheme 5.1** Heck coupling of boronic acids in flow using Pd(OAc)<sub>2</sub> and dppp.

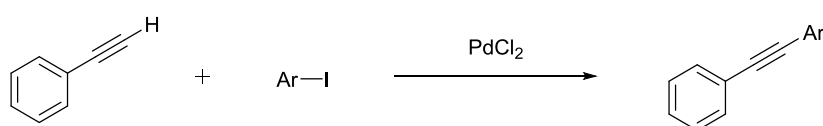
The synthesis of indoles via a tandem amination/Heck coupling has been showcased in flow by Organ et al.<sup>108</sup> To achieve any sort of conversion both a Pd coated capillary and 2.5 mol% of a homogeneous Pd catalyst (PEPPSI-IPr) had to be used. The absence of one or the other resulted in no product formation. A range of substituents were tolerated at the C-2 position and on the aromatic ring (Scheme 5.2), in the presence of *t*-BuONa in toluene at 215 °C, albeit with a relatively long residence time of 78 min.



**Scheme 5.2** Indoles formed via cascade amination/Heck coupling protocol in flow.

### 5.2.3 Sonogashira coupling

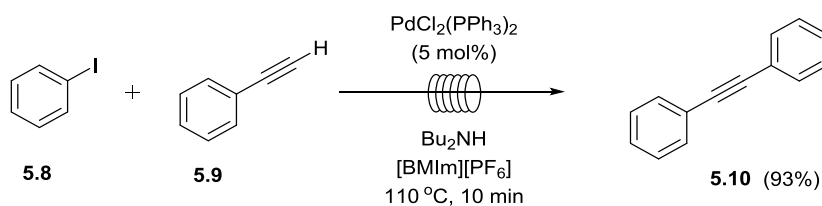
An efficient continuous flow methodology for copper-free Sonogashira couplings reported by Kawanami and Ikushima taking advantage of a high pressure high temperature water (HPHT-H<sub>2</sub>O) reaction medium to promote rapid reaction times.<sup>99</sup> Employing a PdCl<sub>2</sub> (2 mol%) catalyst coupling of aryl iodides with phenylacetylene was achieved in excellent yields in residence times of less than 1 s, at 250 °C and a 16 MPa pressure (Table 5.4). HPHT-H<sub>2</sub>O provides excellent mixing and completely dissolves all of

**Table 5.4** Sonogashira coupling of aryl halide and phenylacetylene in flow.

| Entry <sup>[a]</sup> | Ar-I | Time (s) | Yield (%) |
|----------------------|------|----------|-----------|
| 1                    |      | 4        | 99        |
| 2                    |      | 0.1      | 90        |
| 3                    |      | 0.1      | 91        |
| 4                    |      | 0.1      | 92        |
| 5                    |      | 0.1      | 88        |
| 6                    |      | 0.1      | 99        |
| 7                    |      | 0.1      | 98        |
| 8                    |      | 1.0      | 81        |

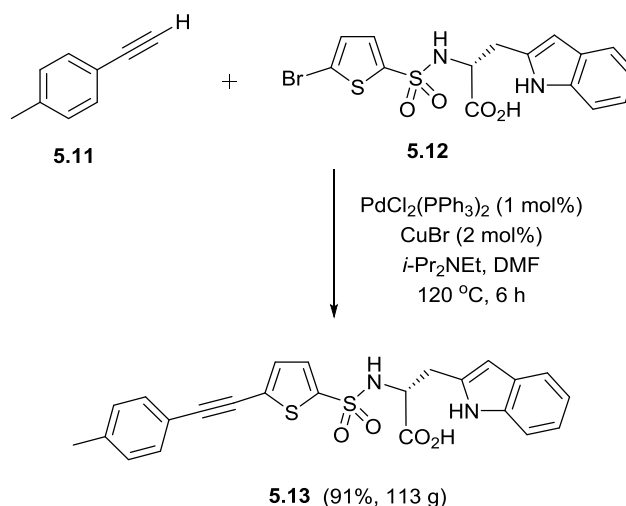
[a] Reaction conditions: PdCl<sub>2</sub> (2 mol%), aq. NaOH, H<sub>2</sub>O, 16 MPa, 250 °C, using a step-by-step rapid mixing and heating approach.

the reagents, negating the need for organic solvents. It was also postulated that hydrogen bonding occurs between the terminal acetylinic hydrogen and H<sub>2</sub>O, thus lowering the activation energy, speeding up the reaction and negating the need for a Cu co-catalyst. In addition to water, ionic liquids are also seen as potential alternatives to organic solvents and as such Ryu et al. devised a flow system for copper-free Sonogashira couplings in an ionic liquid.<sup>109</sup> They used [BMIm][PF<sub>6</sub>] as the solvent of choice and proceeded to couple phenyliodide **5.8** and phenylacetylene **5.9** using a micromixer from which the reaction solution was continuously removed (Scheme 5.3). With PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%) as the catalyst and Bu<sub>2</sub>NH the base at 110 °C, a 93% yield of **5.10** was obtained in a 10 min residence time. After extraction of the product **5.10** and ammonium salts with hexane/water, the [BMIm][PF<sub>6</sub>]/PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> solution was reused up to 3 times, with yields gradually decreasing to 63% for the final run.



**Scheme 5.3** Sonogashira coupling in flow in an ionic liquid.

Reaction scale-up in batch can often be problematic. However in flow, scale up of a process can be achieved by simply running the reactor for longer periods of times or using more reactors. Scale up of a Sonogashira coupling in flow was achieved by Fukuyama and co-workers for the production of a matrix metalloproteinase inhibitor (Scheme 5.4).<sup>110</sup> Compound **5.13** was synthesised on a 100 g scale from **5.12** and tolylacetylene **5.11** with a residence time of 20 min, in the presence of  $\text{PdCl}_2(\text{PPh}_3)_2$  (1 mol%),  $\text{CuBr}$  (2 mol%) and *i*- $\text{Pr}_2\text{NEt}$  at 120 °C in DMF. The system was run continuously for 6 h and gave an overall yield of 113 g (91%).

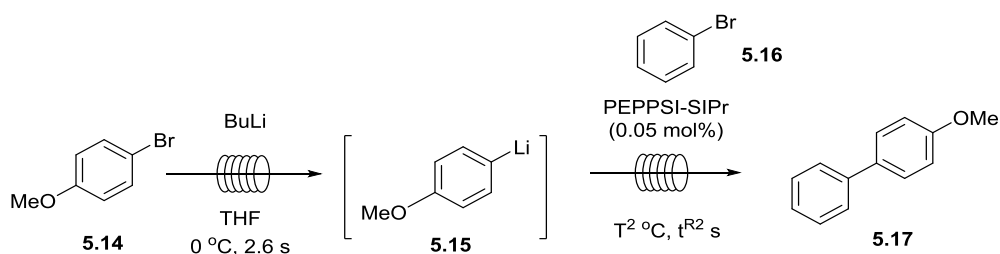


**Scheme 5.4** 100 g scale production of a metalloproteinase inhibitor in flow.

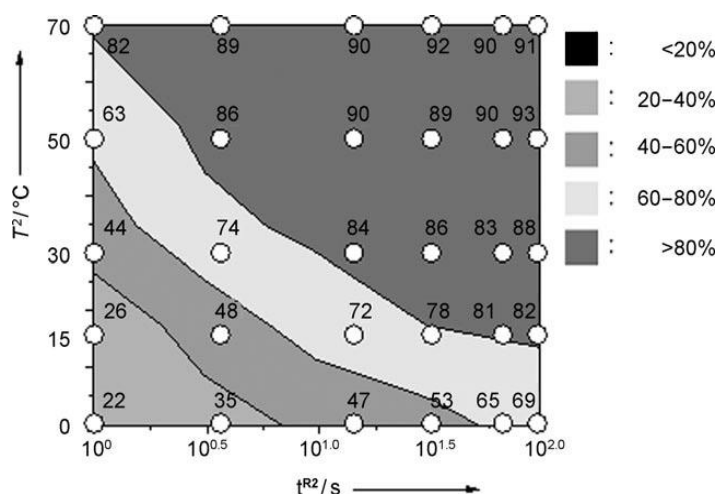
#### 5.2.4 Murahashi coupling

The Murahashi coupling between an aryllithium and aryl halide in continuous flow has been demonstrated by Yoshida et al.<sup>111</sup> The aryllithium **5.15** is generated in situ from an

aryl halide and butyl lithium, thus flow processing is ideal for reactions involving this short-lived species. Lithium-halogen exchange of *p*-bromoanisole **5.14** prior to Pd catalysed coupling with bromobenzene **5.16** (Scheme 5.5) was used as a model reaction for obtaining optimal flow conditions, with PEPPSI<sup>TM</sup>-SIPr as the catalyst for the coupling step, in THF. As shown in Figure 5.3 the yield of **5.17** varies linearly with both residence time and temperature, and the optimum conditions lie in a compromise of the two. A variety of biaryls were generated in yields ranging between 59-93% at 50 °C and with a residence time of 94 s. This protocol was then extended to the coupling of vinylhalides, with substantially shorter residence times ranging from 6-26 s.<sup>112</sup> The analogous Kumada coupling has also been utilised in flow by Styring<sup>113</sup> with the aid of a supported nickel catalyst, although to date this has not been demonstrated with the use of Pd.



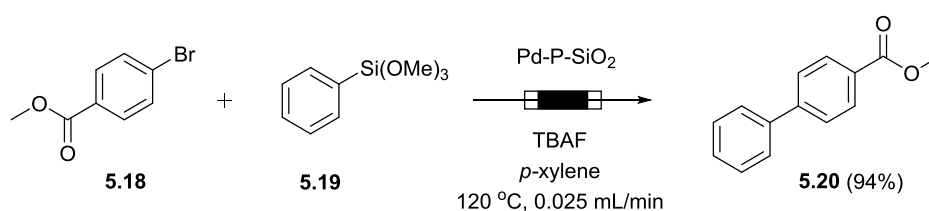
**Scheme 5.5** Murahashi coupling in flow.



**Figure 5.3** Effect of temperature ( $T^2$ ) and residence time ( $t^{R2}$ ) on conversion of intermediate **5.15** to **5.17** (Yoshida et al.) (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission<sup>111</sup>).

### 5.2.5 Hiyama coupling

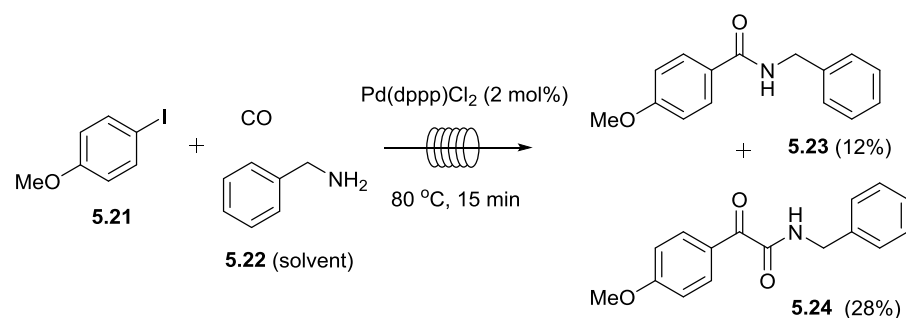
The Hiyama coupling of aryl bromides such as **5.18** and trimethoxyphenylsilane **5.19** has been conducted in flow by Song et al.<sup>114</sup> A silica supported phosphane palladium complex (Pd-P-SiO<sub>2</sub>) was used to give good to excellent conversions for a range of aryl and heteroaryl bromides in the presence of TBAF in *p*-xylene, at 120 °C with a flow rate of 0.025 mL/min, although no actual residence time was reported (Scheme 5.6).



**Scheme 5.6** Hiyama coupling of an arylsilane **5.19** in flow.

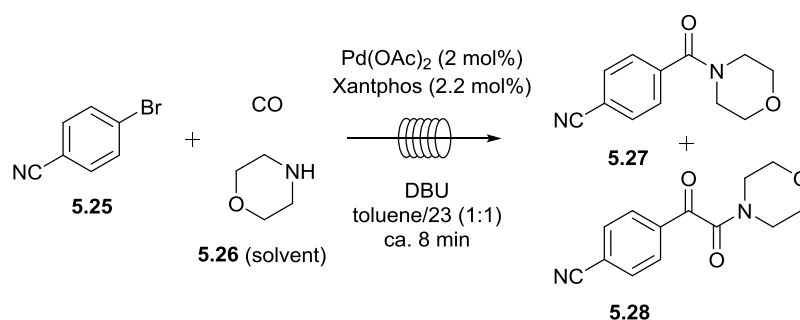
### 5.2.6 Carbonylative couplings

Palladium catalysed carbonylative couplings are an important transformation for the incorporation of carbonyl groups in a regioselective fashion.<sup>115</sup> A microchip flow reactor was fabricated by Miller et al. that operated via an annular flow process, with the gas flowing down the centre of the channel at a faster rate than that of the liquid, which was pushed to outside of the channel.<sup>116</sup> Coupling of aryl halides with benzylamine **5.22** was achieved in moderate yields with a Pd(dppp)Cl<sub>2</sub> catalyst and flow rate of 5 μL/min (15 min residence time). At higher flow rates yields were substantially decreased due to a drop in backpressure of the gas and decrease in contact area between the liquid and gas, which both affect the amount of carbon monoxide dissolved in the liquid phase. They also observed formation of  $\alpha$ -ketoamide product **5.24**, subsequently the major product observed from the reaction with 4-iodoanisole **5.21** (Scheme 5.7), not previously seen in batch operation. This was also attributed to greater amount of dissolved CO in the liquid phase attained by the higher pressure and improved mixing, which was not attainable in batch operation.



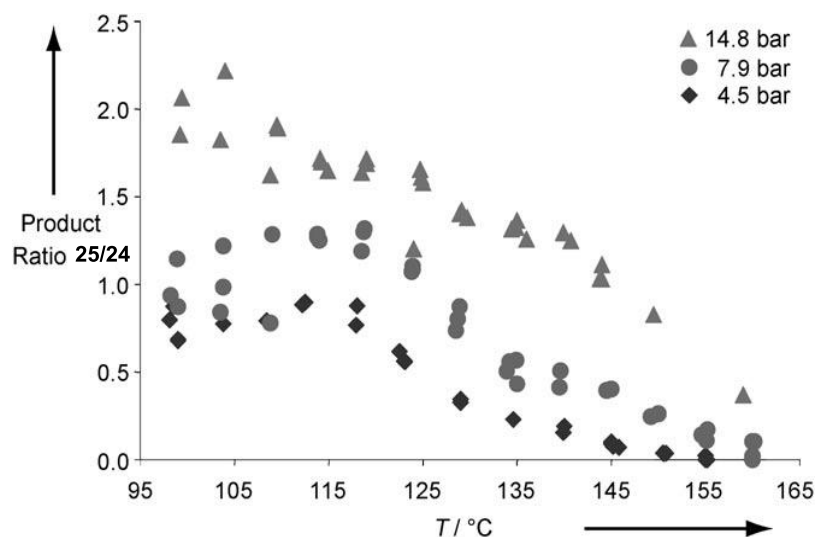
**Scheme 5.7** Formation of an  $\alpha$ -ketoamide via carbonylative coupling in flow.

Buchwald and Jensen then went a step further and studied the effect of carbon monoxide pressure and reaction temperature on  $\alpha$ -ketoamide formation (Scheme 5.8, Figure 5.4).<sup>117</sup> They discovered that higher pressures gave an increased yield of  $\alpha$ -ketoamide **5.28**, while raising the temperature was found to favour the amide product **5.27**. This was in line with Miller's original postulation that at higher pressures, CO insertion competes with nucleophilic attack and undergoes a double carbonylation, while higher temperatures increase the rate of attack by the nucleophile, thus favouring only a single CO insertion.<sup>116</sup>

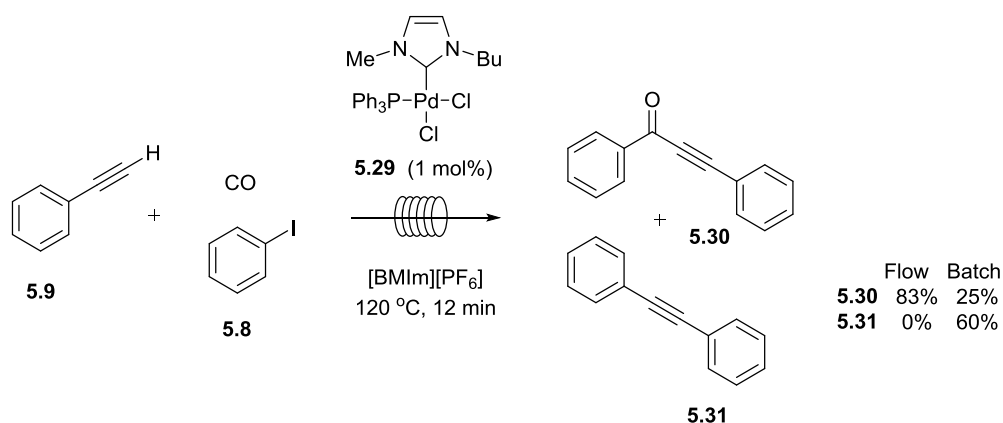


**Scheme 5.8** Carbonylative coupling of morpholine and an aryl halide in flow.

In a similar fashion, Ryu et al. have also demonstrated remarkable selectivity for the formation of  $\alpha,\beta$ -acetylenic ketones such as **5.30**, via carbonylative Sonogashira coupling in flow using an *N*-heterocyclic carbene (NHC) Pd complex **5.29** (Scheme 5.9).<sup>97</sup> This is again attributed to the high CO solubility compared to the equivalent batch process, which yields mixtures of carbonylated and non-carbonylated products.



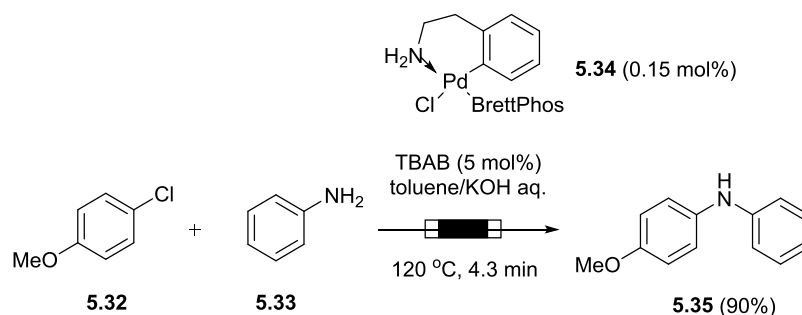
**Figure 5.4** Effect of temperature and pressure on the ratio of mono and dicarbonylated products (Jensen et al.) (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission<sup>117</sup>).



**Scheme 5.9** Improved control of the carbonylative Sonogashira coupling using continuous flow.

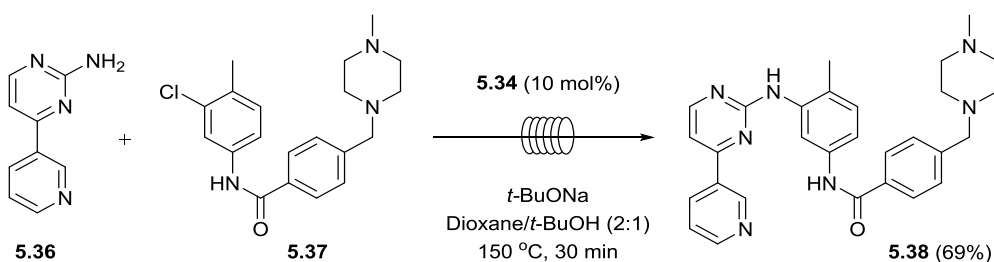
### 5.2.7 Buchwald-Hartwig Amination

The construction of C-N bonds is an important tool for synthesis; however, Pd catalysed Buchwald-Hartwig cross-couplings in flow can be problematic. The formation of inorganic salts as by-products, that are often insoluble in the chosen reaction medium, can precipitate and cause blockages within the microreactor. Buchwald and Naber disclosed a biphasic system of toluene/water, which was shown to prevent precipitation, and hence blockages, by solubilising the organic reaction components and the inorganic by-products.<sup>118</sup> Due to the laminar flow characteristics of microreactor systems, biphasic mixtures typically display poor mixing and have low interfacial surface areas.



**Scheme 5.10** Buchwald-Hartwig amination in flow.

To overcome this they employed TBAB (5 mol%) as a phase transfer catalyst and conducted the reaction in a packed bed reactor consisting of stainless steel spheres (60–125 mm) to ensure vigorous mixing between the two phases. This resulted in excellent yields for the coupling of aryl halides and primary amines using a BrettPhos Pd pre-catalyst **5.34** (0.15 mol%), TBAB and KOH, at 120 °C with a residence time of 4.3 min. When compared to the equivalent conditions under batch operation, continuous flow gave much higher yields in shorter reaction times. Another strategy for dealing with the formation of blockages in flow was described by Buchwald and Jensen using acoustic irradiation to breakup aggregates of solid particles inside the microreactor channels by immersing the reaction channel in an ultrasonic bath, to prevent blockages from occurring.<sup>119</sup> This led to the coupling of aryl chlorides, bromides and triflates with several aryl and alkyl amines, with a Pd BrettPhos pre-catalyst at 60 °C and residence times ranging from 20 s to 5 min. Ley and co-workers recently showcased the synthesis of Imatinib (the API of Gleevec), in flow using a C-N cross-coupling for the final step (Scheme 5.11).<sup>120</sup> They utilised a solvent system of dioxane/*t*-BuOH (2:1) and **5.34** in the presence of *t*-BuONa, to give Imatinib **5.38** in a yield of 69% at 150 °C with a residence time of 30 min.



**Scheme 5.11** Synthesis of Imatinib **5.38** in flow via C-N cross-coupling.



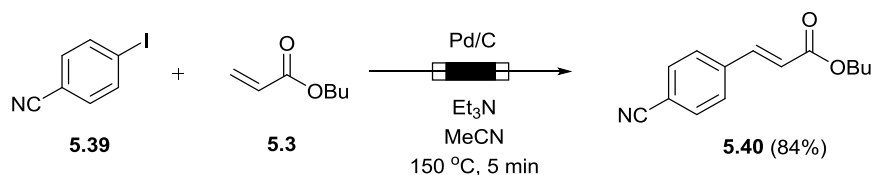
### 5.3 Palladium Catalysts for Flow Systems

There are a wide variety of different catalytic technologies available for conducting cross-couplings in continuous flow. Traditionally heterogeneous systems were favoured due to their ease of separation, recycling and high surface areas making for more efficient processing.<sup>96</sup> However, with issues surrounding leaching of Pd into solution and subsequent loss of activity making their use problematic over extended periods of time, new synthetic strategies based around homogeneous catalysts have been developed, using exceptionally low catalyst loadings, recyclable biphasic systems and ultra-short residence times making them competitive with their heterogeneous counterparts. This section will give an overview of the main catalytic strategies used for Pd catalysed cross-couplings in continuous flow systems.

#### 5.3.1 Heterogeneous Supported Catalysts

##### 5.3.1.1 Palladium on Charcoal

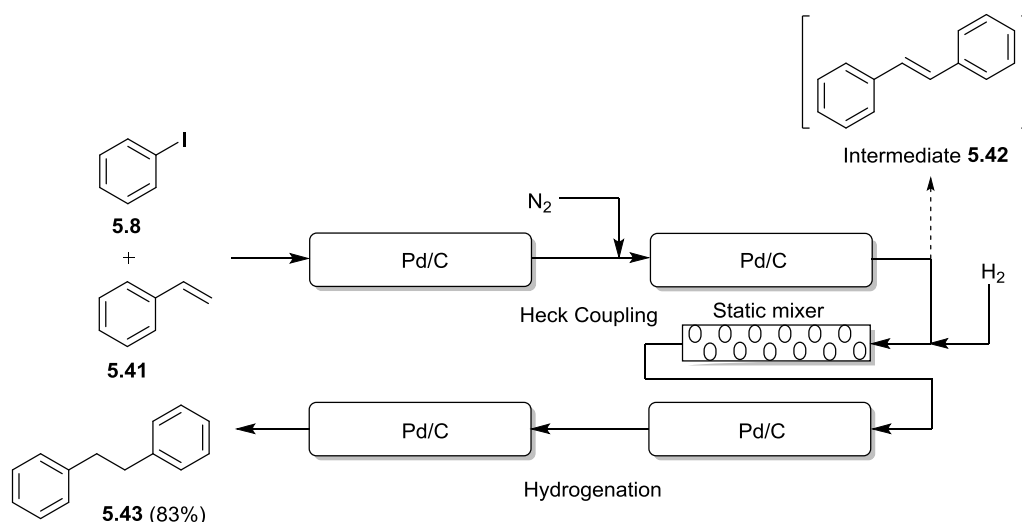
Palladium on charcoal (Pd/C) is one of the cheapest and most widely available palladium catalysts for heterogeneous catalysis.<sup>121</sup> Kappe et al. have utilised Pd/C to promote the Heck coupling of aryl iodide **5.39** with butyl acrylate **5.3** (Scheme 5.12) in flow.<sup>122</sup> The reactions were carried out using pre-packed stainless steel cartridges of the catalyst (60 x 4 mm i.d., ca. 310 mg Pd/C).



**Scheme 5.12** Pd/C catalysed Heck coupling in flow.

Complete conversion of **5.39** was achieved at 150 °C, with a residence time of approximately 5 min in the presence of Et<sub>3</sub>N. Under flow conditions it was found that product **5.40** was accompanied by a significant amount of homocoupling (9%) and

dehalogenated (7%) by-products, in comparison to microwave-batch which gave only trace amounts. The significant amount of dehalogenation was thought to be due to the high catalyst loading employed under continuous flow conditions, which was also observed with high catalyst loadings in batch. This, however, did not account for the homocoupling which was attributed to a chromatographic separation effect exhibited by the packed column. ICP-MS analysis of the used cartridge indicated that 89% of the palladium had leached into the solution after conducting twelve consecutive reactions utilising the same solid support. It was thought that the reaction mechanism involved a quasi-homogeneous Pd species, where the Pd/C was acting as a reservoir for soluble, active Pd species which were constantly undergoing absorption/dissolution.<sup>123</sup> Switching to a homogeneous Pd(OAc)<sub>2</sub> catalyst system, with a long stainless steel coil in place of a cartridge, afforded complete conversion to product at 170 °C and a residence time of 10 min (0.4 mL/min), on par with batch. Plucinski et al. have also demonstrated the use of Pd/C in flow to promote a sequential Heck coupling, hydrogenation protocol in a custom made multichannel flow reactor.<sup>124</sup> The production of 1,2-diphenylethane **5.43** was reported via Heck coupling of styrene **5.41** and iodobenzene **5.8**, followed by hydrogenation of the resulting alkene **5.42** (Scheme 5.13), using 5 wt% Pd/C for both steps. Excellent conversions of 84% and 99% were achieved for both Heck coupling and hydrogenation respectively with a total residence time of 6 min (c.a. 3 min for each step) and an H<sub>2</sub> flow rate of 8 mL/min, at 95 °C.

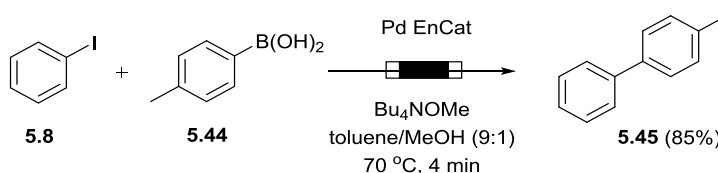


**Scheme 5.13** Sequential Heck coupling/hydrogenation using Pd/C in flow.

However, a significant amount of Pd leaching was observed from the column used for Heck coupling and conversion dropped by c.a. 60% for subsequent runs. Interestingly though it was found that the hydrogenation column could act as a scavenger for palladium leached from the previous column used for cross coupling. The authors devised an alternating forward/reverse reaction strategy, where the order of the columns was swapped after each run so that the leached Pd was consistently re-deposited and both channels remained active. This concept was proven to be effective at maintaining activity and consecutive forward and reverse runs achieved consistently high conversions.

#### 5.3.1.2 Pd EnCat

Ley et al. pioneered the development and use of a polyurea-encapsulated  $\text{Pd}(\text{OAc})_2$  catalyst (Pd EnCat), which is a commercially available heterogeneous palladium catalyst that has become popular for in a wide variety of batch applications.<sup>125</sup> Like other heterogeneous reagents, packing Pd EnCat into a column allows it to be utilised in continuous flow systems. Its use was first documented for the Suzuki coupling of iodobenzene **5.8** and *p*-tolylboronic acid **5.44** (Scheme 5.14).<sup>126</sup> An 85% yield of the biaryl product **5.45** was obtained at 70 °C with a residence time of 4 min. Several bases were investigated, but  $\text{Bu}_4\text{NOMe}$  gave the best results as it afforded a homogeneous reaction mixture which maximised the interaction between reagents and catalyst.



**Scheme 5.14** Pd EnCat catalysed Suzuki coupling in flow.

Leeke et al. further investigated the Suzuki coupling of **5.8** and **5.44** with Pd EnCat in flow, this time on an exploratory commercial scale, utilising both traditional organic solvents and scCO<sub>2</sub>.<sup>127</sup> They observed that, in a conventional solvent system (toluene/methanol 9:1), both reaction temperature and flow rate were significant factors in the conversion. In general higher temperatures afforded higher conversions up to 100 °C, after which this effect was less prominent.

The optimum flow rate was found to be 6.4 mL/min, which afforded a 74% conversion to **5.45**. Any attempt to lower the flow rate and thus increase residence time, afforded lower conversions. This was attributed to poorer mixing due to a lower solid/liquid ratio. At all temperatures and flow rates, homocoupling to the undesirable biphenyl byproduct did not exceed 1.8%. To improve conversion further the reagent solution was passed three times over the column, but this only afforded a slight increase in conversion. It was found that the pH of the reaction mixture dropped from pH 13.4 initially to 7.3 after the first pass. Addition of a further portion of Bu<sub>4</sub>NOMe after the first pass returned the pH to 13.4 and afforded complete conversion to **5.45** on the second pass. The same reaction was examined under scCO<sub>2</sub> conditions, with MeOH as a co-solvent to increase the solubility of the Bu<sub>4</sub>NOMe, shown in Table 5.5. An optimum conversion of 81% was achieved under supercritical conditions at 166 bar and 100 °C, with a reagent flow rate of 5.5 g/min. Raising the pressure showed a decrease in conversion and lowering the pressure afforded satisfactory conversion, although this resulted in a two-phase liquid-vapour reaction system (effectively utilising a CO<sub>2</sub> expanded solvent system).<sup>128</sup>

**Table 5.5** Pd EnCat catalysed Suzuki coupling in flow under scCO<sub>2</sub> conditions.

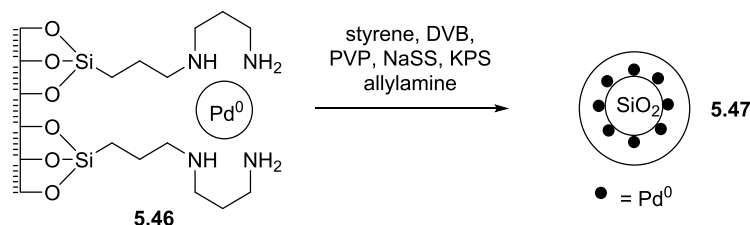
| Entry <sup>[a]</sup> | <i>P</i> (bar) | <i>T</i> (°C) | Phase              | Flow rate<br>(mL/min) | CO <sub>2</sub> :MeOH<br>ratio | Conversion<br>(%) |
|----------------------|----------------|---------------|--------------------|-----------------------|--------------------------------|-------------------|
| 1                    | 150            | 80            | sc                 | 4.5                   | 15:1                           | 21                |
| 2                    | 150            | 80            | sc                 | 2.5                   | 29:1                           | 38                |
| 3                    | 166            | 100           | sc                 | 2.0                   | 24:1                           | 39                |
| 4                    | 150            | 80            | sc                 | 4.8                   | 7:1                            | 6                 |
| 5                    | 150            | 80            | sc                 | 4.5                   | 6:1                            | 9                 |
| 6 <sup>[c]</sup>     | 102            | 100           | L/V <sup>[b]</sup> | 5.5                   | 10:1                           | 65                |
| 7 <sup>[c]</sup>     | 110            | 100           | L/V <sup>[b]</sup> | 5.5                   | 10:1                           | 74                |
| 8 <sup>[c]</sup>     | 166            | 100           | sc                 | 5.5                   | 10:1                           | 81                |
| 9 <sup>[c]</sup>     | 168            | 100           | sc                 | 5.5                   | 70:1                           | 21                |
| 10 <sup>[c]</sup>    | 167            | 100           | sc                 | 5.5                   | 145:1                          | 20                |
| 11 <sup>[c]</sup>    | 186            | 100           | sc                 | 5.5                   | 10:1                           | 75                |
| 12 <sup>[c]</sup>    | 208            | 100           | sc                 | 5.5                   | 10:1                           | 73                |
| 13 <sup>[c]</sup>    | 250            | 100           | sc                 | 5.5                   | 10:1                           | 70                |

[a] Reaction conditions: **38**, **26**, Pd EnCat packed into a column of length 48.5 cm, Bu<sub>4</sub>NOMe (1.1 eq.), scCO<sub>2</sub>, MeOH. [b] Biphasic liquid-vapour system [c] Column length 22.5 cm.

Operating at lower pressures could provide advantages in process economics upon scale up. Initially it was thought that palladium leaching from Pd EnCat under continuous flow conditions was negligible, with ICP-MS analysis indicating palladium levels of 10 ppm (0.025% metal loss) in the filtered reagent solution.<sup>129</sup> However, as shown by Broadwater and McQuade, when a more complex 3-phase test was conducted significant leaching was found to be occurring in the form of a soluble Pd species, thus the Pd EnCat was serving as a Pd reservoir.<sup>130</sup> It was concluded that a significant amount of the reaction was occurring in solution, mediated by this soluble active Pd species, but that a true heterogeneous catalytic system could also be occurring.

### 5.3.1.3 Silicon Dioxide Supports

Silicon dioxide ( $\text{SiO}_2$ ) is a common support for heterogenised catalysis.<sup>131</sup> It is cheap, abundant, non-toxic and has excellent thermal stability, which make it widely accessible for a variety of catalytic applications although to-date, its use for palladium catalysed couplings in flow is limited. Frost and co-workers have described the preparation and use of a novel silica-supported polymer-encapsulated Pd catalyst **5.47** (Scheme 5.15) for both Suzuki and Heck couplings in flow.<sup>132</sup> Pd was first supported onto surface functionalised amorphous silica (**5.46**), before being subjected to a polymerisation of styrene, divinylbenzene (DVB) and allyl amine to form spherical particles with a porous copolymer coating.

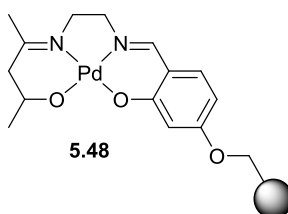


**Scheme 5.15** Preparation of silica-supported polymer-encapsulated Pd catalyst.

The reagent solutions were pumped over an Omnifit column,<sup>133</sup> packed with a mixture of the supported Pd catalyst and sand (100 x 6 mm, ca. 200 mg catalyst, 1.5 g sand). Suzuki couplings of aryl iodides and phenylboronic acid in the presence of DIPEA, were conducted at 120 °C with residence times of 20-50 min. This gave good to excellent conversions for both electron rich and electron poor aryl iodides. Heck coupling of the same aryl iodides with styrene was also demonstrated. These were conducted at 140 °C with residence times of 80-100 min and gave slightly lower conversions. The need for relatively long residence times was attributed to the need for the reagents to diffuse across the porous polymer coating before coupling could occur. However, this was offset by low levels of Pd leaching (0.05% Pd per run, measured by ICP-MS). The same batch of catalyst was reused for over 50 runs with no appreciable change in the structure or decrease in activity of the catalyst.

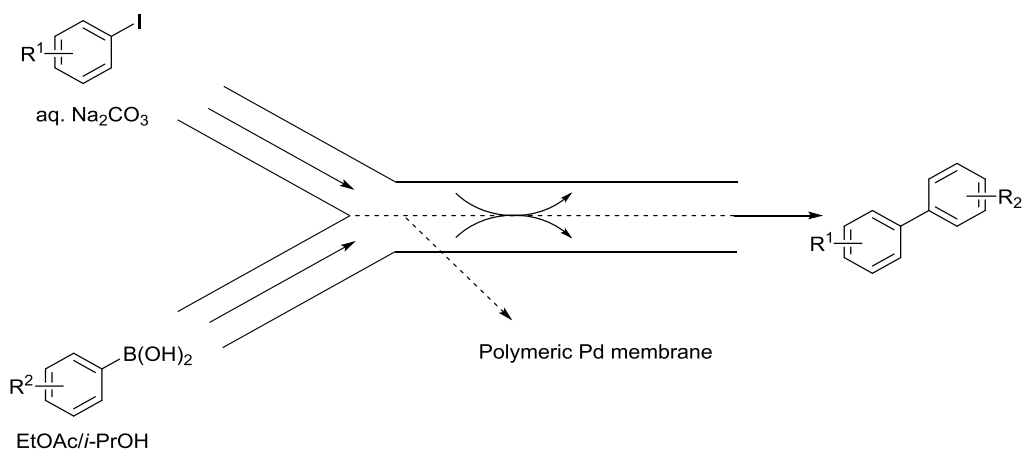
#### 5.3.1.4 Polymeric Supports

Styring and co-workers have developed a polymer supported Pd catalyst for Suzuki couplings.<sup>134, 135</sup> The catalyst is based on a Pd<sup>II</sup> salen type complex supported on polystyrene–DVB crosslinked Merrifield resin beads (Scheme 5.16). The supported Pd complex **5.48** was loaded into an Omnifit column<sup>133</sup> (25 mm x 3 mm) and connected to a syringe pump by PTFE tubing (i.d. 0.8 mm). The column was heated via immersion in a water bath. Care was taken to ensure homogeneity of the reaction mixture throughout the process. The optimal conditions for Suzuki coupling of an aryl bromide with a slight excess of phenylboronic acid were found to be 100 °C with a residence time of 10.5 min using DIPEA as the base in a solvent mixture of DMF/Water (1:1).



**Scheme 5.16** Pd<sup>II</sup> salen complex supported on Merrifield resin beads.

Moderate to good conversions were obtained for a diverse range of substrates including heteroaromatic and CO<sub>2</sub>H, CN and SO<sub>2</sub>Me substituted aryl bromides. In an attempt to improve the conversion the authors employed the so-called ‘stopped flow technique’ previously demonstrated by Wiles et al.<sup>136</sup> in which a 10 min period of flow was alternated with a fixed period in which flow was stopped, before restarting flow for another 10 min. This has the effect of increasing the apparent residence time without lowering the flow rate. Using an initial stopped flow period of 5 min improved the conversion slightly to 76% and increasing the time gave a linear increase in conversion up to 86% for 20 min, with no by-products observed in any of the runs. In contrast to the packed bed approach, Uozumi et al. prepared a polymeric Pd membrane inside a microreactor channel and showcased its use in catalysing Suzuki couplings.<sup>137</sup> Using a microreactor with a Y-shaped dual inlet, they flowed opposing solutions of the polymer (poly(*N*-isopropylacrylamide)<sub>5</sub>-co-(4-diphenylstyrylphosphine)) in EtOAc and the Pd



**Figure 5.5** – Suzuki coupling in flow catalysed by polymeric Pd membrane at the biphasic interface.

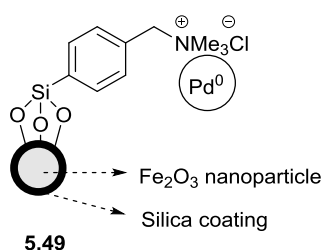
source ( $\text{PdCl}_4(\text{NH}_4)_2$ ) in water, into the microchannel at 25 °C with a flow rate of 25 mL/min. This formed a two-phase laminar flow, at the interface of which the Pd polymer membrane was precipitated. Suzuki couplings were conducted in a biphasic fashion with solutions of aryl iodide in ethyl acetate/isopropyl alcohol (2:5) and arylboronic acid in aqueous  $\text{Na}_2\text{CO}_3$  introduced into the two channels, once again with laminar flow, separated by the catalytic membrane at which the reaction took place (Figure 5.5). This afforded good to excellent yields for the synthesis of biaryls. Quantitative conversion was achieved for a variety of aryl iodides and boronic acids with short residence times of 4-5 s at 50 °C. ICP-AES analysis showed minimal Pd leaching from the membrane into the reagent streams. An added advantage of this process is that the biphasic laminar flow allows for in-line separation of the products from the aqueous base and salt by-products.

### 5.3.1.5 Magnetic Nanoparticles

There has been increasing interest in the use of magnetic nanoparticles as solid supports for heterogeneous catalysts,<sup>138, 139</sup> stemming from their facile post-reaction recovery by application of an external magnetic field.<sup>140</sup> As with silica and polymeric supported catalysts, the magnetic nanoparticles can be functionalised to facilitate metal ligation. For palladium containing nanoparticles amine moieties are often used as they prevent aggregation of the Pd reducing the formation of Pd black and increasing the reactivity of



the catalyst.<sup>141</sup> A prominent example of their use in flow was disclosed by Kirschning et al. who prepared Pd functionalised, silica coated Fe<sub>3</sub>O<sub>4</sub>/Fe<sub>2</sub>O<sub>3</sub> nanoparticles **5.49** (10-40 nm), which were used for Suzuki and Heck couplings under flow conditions.<sup>142</sup> An added advantage of these particles is their superparamagnetic behaviour, which allows them to be heated via magnetic induction when subjected to an electromagnetic field. This was exploited as a way of heating the flow reactor remotely and allowing heat to be generated directly at the reaction site inside the reactor.



**Scheme 5.17** Silica coated magnetic nanoparticle functionalised with Pd.

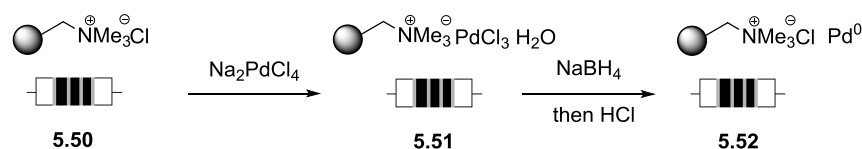
The silica coating on the surface of the magnetic nanoparticles prevents oxidation of the highly reactive metallic surface in air and also allows for easy functionalisation and transition metal loading. The Catalyst (2.8 mol% loading) was utilised in both the Suzuki and Heck coupling reactions. The Suzuki coupling of *p*-bromoacetophenone and phenyl boronic acid, in the presence of CsF in DMF:H<sub>2</sub>O afforded a 77% isolated yield of the desired product. This was achieved with a residence time of 1 h at 100 °C. The Heck coupling between *p*-iodoacetophenone and styrene in the presence of Bu<sub>3</sub>N in DMF afforded a 76% isolated yield, again with a residence time of 1 h, at 120 °C. ICP-MS analysis revealed only low levels of palladium leaching was occurring (34 ppm for the Suzuki-Miyaura coupling and 100 ppm for the Heck) and the catalyst could be reused for more than three runs with no loss of activity.

### 5.3.1.6 Monolithic Supports

Monolithic flow reactors are based on a polymer bound reagent encased within a cartridge which exhibit low to moderate pressure drops.<sup>143</sup> They consist of small polymeric beads (1-5 mm diameter) that are cross-linked with polymer bridges.<sup>144</sup> As such monolithic supports can be described as comprising of interconnected repeating cells or channels with excellent mass transfer properties.<sup>145</sup> One of the earlier pioneers of this reaction medium was Kirschning who termed this a PASSflow (polymer assisted solution-phase synthesis) technique. The group developed a reactor system consisting of a monolithic block based on a highly porous polymer/glass composite material.<sup>146</sup> This composite was made up of a copolymer of benzyl chloride crosslinked with DVB, inside porous glass rods. The addition of triethylamine to this vinylbenzyl chloride polymer resulted in the formation of quaternary ammonium ions (for an example of the quaternary ammonium ions see Scheme 5.18), to which Pd was coordinated. This reactor has been utilised to perform the Heck, Suzuki and Sonogashira coupling reactions in excellent yields with residence times ranging from 30 min - 3 h.<sup>147</sup> Ley et al. have also prepared palladium supported monoliths to catalyse the Heck reaction.<sup>148</sup> Their monolithic support was constructed using vinylbenzyl chloride (35%), cross-linked with divinylbenzene (20%) and with 1-dodecanol (45%) being employed as the porogen, within Omnifit glass columns<sup>133</sup> (70 mm, 6.6 mm i.d.). A variety of aryl iodides and alkenes were examined utilising DMF as the reaction solvent in the presence of triethylamine at 130 °C. At 0.05 mL/min each reaction carried out afforded 100% conversion with isolated yields ranging from 82 to 87%. Unfortunately, aryl chlorides were unreactive under these conditions. Due to the toxicity and difficult removal of DMF an alternative solvent was

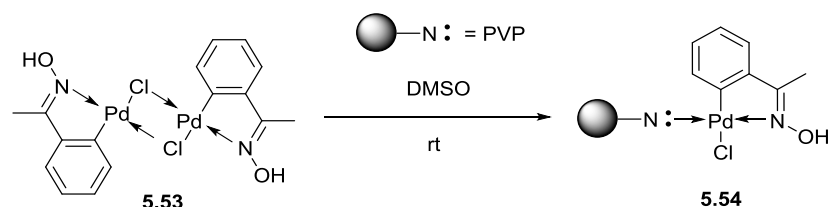


**Figure 5.6** Raschig rings aligned on a perforated tube, within a PEEK polymer casing. (Kirschning et al.) (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission<sup>149</sup>).



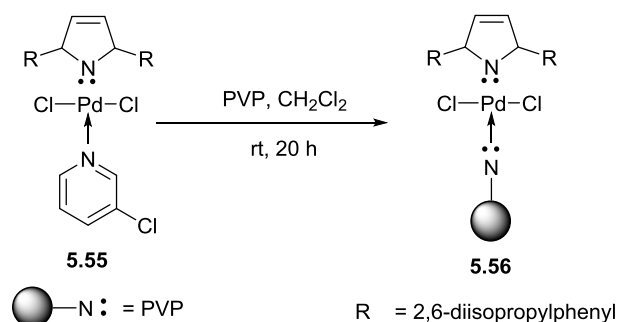
**Scheme 5.18** Raschig rings functionalised with Pd, via quaternary ammonium ions.

sought that could also carry out the reaction at 130 °C. It was found that superheating EtOH at elevated pressure, by using an in-line 100 psi back pressure regulator, afforded similar results to those obtained using DMF. ICP-MS analysis on the isolated solid products indicated a very high level of Pd contaminate (270 ppm). This was resolved by inserting an on line, thiourea based metal scavenger resin (Quadrature™ TU)<sup>150</sup> prior to compound collection. The Pd levels within the solid product was reduced to below 5 ppm.<sup>148</sup> Kirschning et al. further expanded the use of monoliths by incorporating them inside Raschig rings.<sup>149, 151</sup> The Raschig ring reactor has the advantage over a rod-type reactor as it can be easily unscrewed and the spent rings removed and replaced with newly functionalised rings.<sup>152</sup> These reactors are adaptable being utilised for small scale reactions (only one ring) as well as larger scales. The rings can be prepared in large quantities, making them more economically viable than rod shaped reactors.<sup>153</sup> Figure 5.6 illustrates the separate components of the Raschig ring reactor.<sup>149</sup> Kirschning et al. carried out precipitation polymerisation within Raschig rings utilising styrene, divinylbenzene and vinylbenzyl chloride (2.3%) as monomers. Washing through with triethylamine formed the quaternary ammonium ion **5.50**, as previously described. Palladium can be anchored onto this solid support by means of ion exchange **5.51** by pumping sodium tetrachloropalladate through the ring. The active palladium species **5.52** can then be formed by reduction with sodium borohydride (Scheme 5.18). This afforded nanoparticles of 7 to 10 nm in size with a palladium content of 0.003 wt%.<sup>154</sup> This catalyst was then utilised in both the Suzuki and Heck cross coupling reactions. It was found that the catalyst showed excellent stability without loss of activity even after the tenth run. For each run the palladium leaching was determined to be in the region of 0.7 ppm. In a further study the Raschig rings were coated in PVP and cross linked with 5.3% DVB, to which catalyst **5.53** was coordinated to create a monolith with irregular microchannels (50 mm) (Scheme 5.19). It was suggested that catalyst **5.54** acts as a reservoir for palladium nanoparticles, of an unspecified nature, which are formed after reduction. It

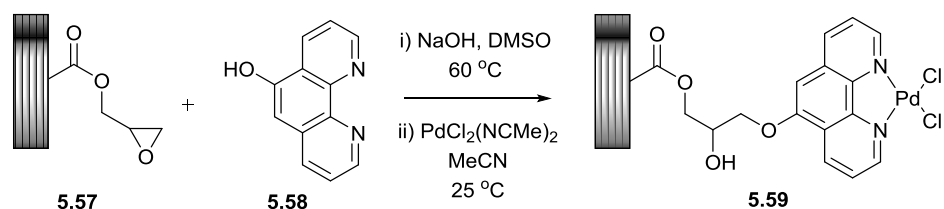


**Scheme 5.19** Preparation of Pd catalyst via coordination to PVP monolith inside Raschig rings.

was further speculated that the  $\text{Pd}^0$  species can either catalyse reactions, or re-coordinate onto the PVP support. This solid supported catalyst was utilised in both Suzuki- Miyaura and Heck reactions. De Vries had noted that at temperatures between 100 and 150 °C the mechanism of the ligand-free palladium-catalysed Heck reaction changed, which could cause the deposition of Pd black.<sup>155</sup> It was shown that only a small amount of palladium leaching was observed, with 1.1 to 2.1 ppb being present after the reaction has cooled. It is possible that the PVP is acting as a  $\text{Pd}^0$  reservoir, which exerts its reactivity in solution. The low degree of leaching can be attributed to the fact that there are numerous free pyridine sites in PVP that can efficiently scavenge and retard the formation and growth of colloids. When a palladium scavenger is in operation, for example a thiol, then any palladium in solution that becomes trapped in this scavenger is completely deactivated. If, however, the PVP is utilised as the scavenger a palladium species can be created that still exhibits catalytic activity. This idea was extended further to incorporate a PEPPSI complex **5.55** onto a PVP support within a Raschig ring (**5.56**, Scheme 5.20).<sup>156</sup> Guijt et al. have also utilised phenanthroline functionalised poly(glycidyl methacrylate-*co*-ethylene dimethacrylate) (GMA-*co*-EDMA) **5.57** as a solid macroporous monolith to support palladium to give **5.59**, which was used as a catalyst for Suzuki reactions (Scheme 5.21).<sup>157</sup>



**Scheme 5.20** Preparation of a PVP coordinated PEPPSI complex.

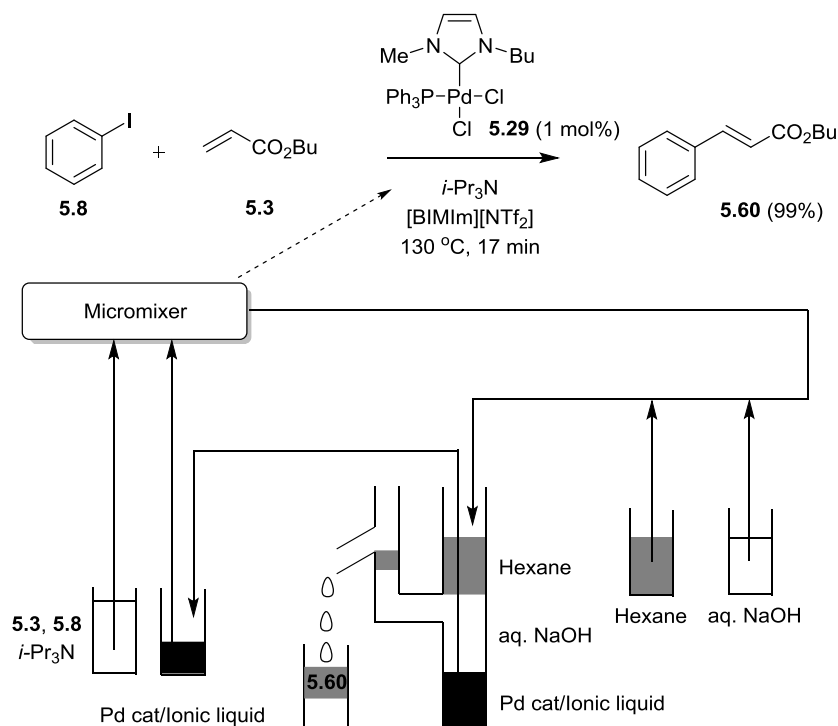


**Scheme 5.21** Preparation of  $\text{PdCl}_2$  supported on a phenanthroline functionalised monolith.

### 5.3.2 Homogeneous Catalysts

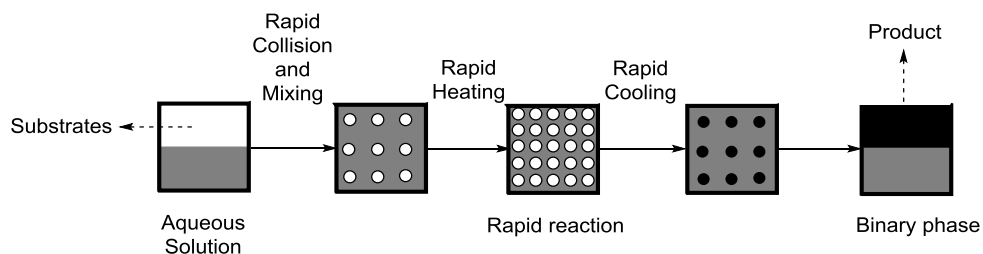
#### 5.3.2.1 Single Phase Reactions

Catalyst systems used for homogeneous single phase cross-couplings are often analogous to those chosen for conventional batch processes. Many homogeneous Pd catalysts have been utilised in flow including  $\text{Pd}(\text{dppp})\text{Cl}_2$ ,<sup>116</sup>  $\text{Pd}(\text{OAc})_2$ ,<sup>158-160</sup>  $\text{Pd}(\text{PPh}_3)_4$ ,<sup>106</sup> PEPPSI analogues<sup>108</sup> and various phosphane Pd precatalysts,<sup>119, 120</sup> among others. The main disadvantage with single phase homogeneous systems is the afore mentioned issue of catalyst separation



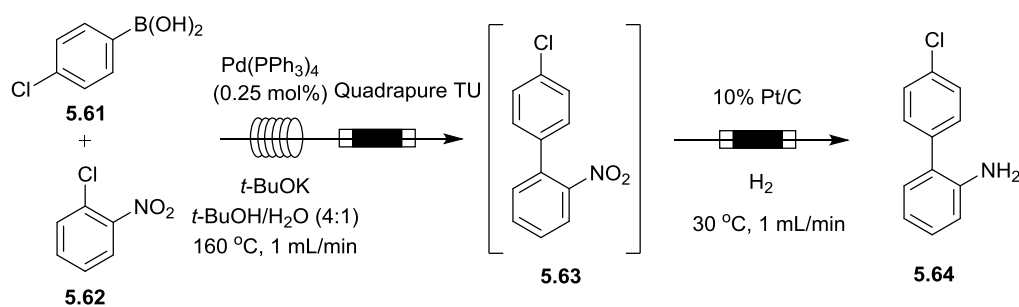
**Figure 5.7** Recycling of a homogeneous Pd catalyst in flow using an ionic liquid based system.

and reuse. Ryu et al. devised one solution to this problem by using an ionic liquid as the reaction solvent in a closed loop system and implementing a continuous extraction technique to remove the product (Figure 5.7).<sup>161</sup> They employed a Pd-carbene complex **5.29** as the catalytic species solubilised in a low viscosity ionic liquid for the Heck coupling of iodobenzene **5.8** and butyl acrylate **5.3**, with a residence time of 17 min at 130 °C. The coupled product was extracted with hexane and the ionic liquid subjected to an aqueous wash to remove the salt byproduct, before being recycled. They have also employed this technique for the Sonogashira coupling.<sup>109</sup> Water is often seen as being an ideal reaction medium for synthetic transformation, but suffers from an inability to solubilise most organic materials. An elegant approach to using water for coupling reactions in flow was conceived by Kawanami and Ikushima.<sup>99</sup> They devised a high-pressure high-temperature strategy (HPHT-H<sub>2</sub>O), as shown in Figure 5.8, with a homogeneous PdCl<sub>2</sub> catalyst for the copper-free Sonogashira coupling. At a pressure of 16 MPa and temperatures of 250-300 °C, good to excellent yields were obtained in exceedingly short residence times of <1-4 s (see section 5.2.3 for the range of substrates).



**Figure 5.8** Rapid mixing and reaction promoted by a HPHT-H<sub>2</sub>O system.

Kappe et al. incorporated the use of a homogeneous system in their sequential synthesis of 2-amino-4'-chlorobiphenyl **5.64**, an intermediate in the synthesis of Boscalid (Scheme 5.22). Suzuki coupling of 1-chloro-2-nitrobenzene **5.62** with 4-chlorophenylboronic acid **5.61** facilitated by Pd(PPh<sub>3</sub>)<sub>4</sub>, was afforded in 89% yield in a *t*-BuOH/H<sub>2</sub>O (4:1) solvent system, with a residence time of 16 min at 160 °C. They also showed that the use of a biphasic THF/H<sub>2</sub>O system, with the addition of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst, gave the same excellent yield. The reaction mixture was then passed over a Quadrapure™ TU (thiourea) scavenger cartridge to remove the Pd(PPh<sub>3</sub>)<sub>4</sub>,

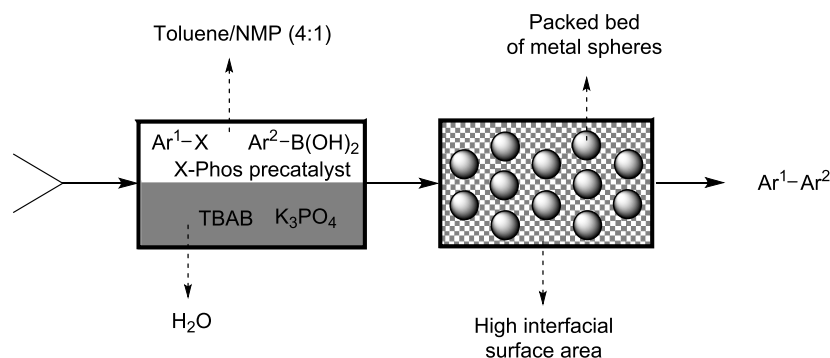


**Scheme 5.22** Synthesis of an **5.64** intermediate of Boscalid via  $\text{Pd}(\text{PPh}_3)_4$  catalysed Suzuki coupling.

prior to a Pt/C catalysed reduction of the nitro group in **5.63**, to give a quantitative yield of the corresponding amine **5.64**.

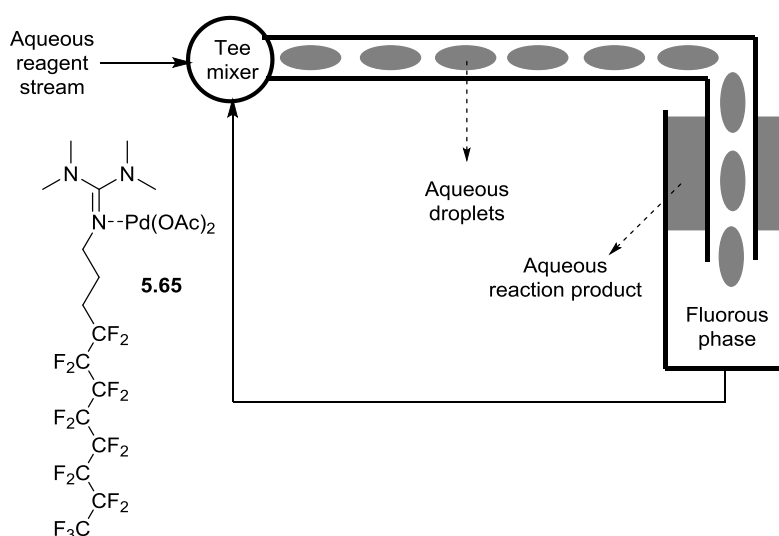
### 5.3.2.2 Biphasic Systems

Biphasic reaction systems can aid post reaction separation and help to maintain the solubility of organic and inorganic species during the reaction itself, which is often a major concern in continuous flow systems where precipitation can cause clogging of the reactor. Noel and Musacchio reported a biphasic protocol using a solvent mixture of NMP/toluene/ $\text{H}_2\text{O}$  (4:1:5) and exceptionally low (0.05-1.5 mol%) loadings of an X-Phos pre-catalyst to facilitate Suzuki couplings.<sup>104</sup> Key to the protocol was efficient mixing inside the flow reactor, facilitated by running the biphasic system over a packed bed of stainless steel spheres, which enabled high levels of mixing to be achieved and raised the interfacial contact between the phases (Figure 5.9).



**Figure 5.9** High interfacial surface area facilitated by excellent mixing in a packed bed.

Near quantitative conversions were obtained for the majority of heteroaryl substrates with a residence time of 3 min at 90 °C. Significant amounts of protodeboronation were found to occur for several 5-membered 2-heteroarylboronic acids, attributed to the relatively high temperature. When the temperature was dropped to 60 °C excellent yields were obtained with 2-thienyl- and 2-furanylboronic acids, at the same low catalyst loadings, by lengthening the residence time to 5 min. Naber and Buchwald have also demonstrated this technique for use in the Buchwald-Hartwig amination.<sup>118</sup> Another approach to ensuring efficient mixing of a biphasic system was developed by Theberge and co-workers using an aqueous/fluorinated solvent system with a fluorous-tagged Pd(OAc)<sub>2</sub> catalyst **5.65**.<sup>162</sup> The two phases were fed dropwise into the flow system via a Tee mixer which created a series of aqueous droplets suspended in the fluorous phase (Figure 5.10). This gave high surface area contact between the two phases and allowed for the Suzuki coupling of 4-bromophenols and 4-bromobenzoic acids, with phenyl- and tolylboronic acid, in good yields at room temperature, albeit with relatively long residence times of 1-3 hours. Due to the ease of separation of the products in the aqueous phase from the catalyst in the fluorous phase, the catalyst could be recycled continuously within the closed-loop flow reactor with minimal Pd leaching into the aqueous phase, as measured by ICP-MS.



**Figure 5.10** Recycling of a fluorous tagged Pd catalyst **5.65** in a biphasic flow system.

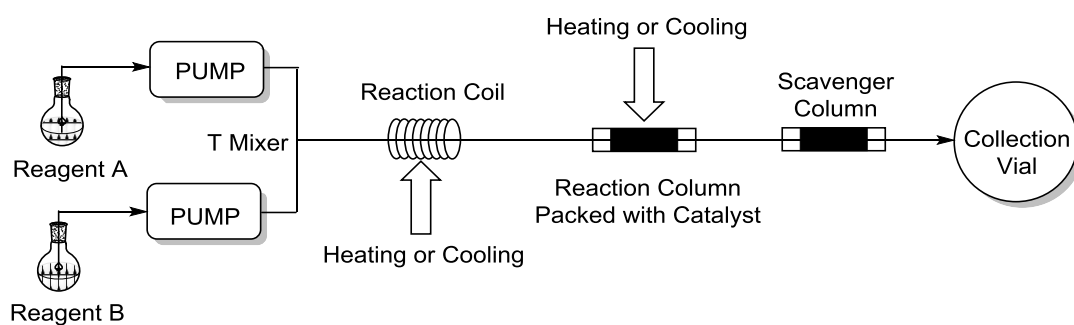


## 5.4 Continuous Flow Technologies for Cross-coupling

### 5.4.1 Microreactors

In recent years, significant advancements have been made in the development of commercially available lab-scale flow reactor technologies. Typically these systems are comprised of well defined reaction channels, usually made of silicon, glass, stainless steel, ceramics or polymers.<sup>163</sup> The majority of continuous flow reactors reported for use on a lab scale have channel dimensions in the order of  $<1000\ \mu\text{m}$  i.d. and are termed 'microreactors'.<sup>13</sup> On the other hand, meso-scale continuous flow reactors possess channel dimensions of  $>1\ \text{mm}$  i.d.<sup>100, 164</sup> The distinction between the two is not always apparent and leads to the term 'microreactor' often being used as an overarching definition of microfluidic systems reported for synthesis. On this scale, laminar or 'plug' flow is the dominant process and mixing within the channels occurs solely via diffusion phenomena<sup>165, 166</sup> allowing for highly predictable, uniform reaction environments, while the high surface to volume ratio allows for precise temperature control and excellent mass transfer properties.

For synthetic applications these channels are connected to a series of reservoirs containing reagents and/or solvent. Flow rates can be anywhere from  $0.01 \sim 10\ \text{mL/min}$ , controlled using standard HPLC or syringe type pumps. Reaction environments can vary depending on application but usually consist of either a length of coiled tubing, common for homogeneous mixtures, or a column that can be packed with a solid material for heterogeneous multiphase applications, the latter allowing for facile separation. These

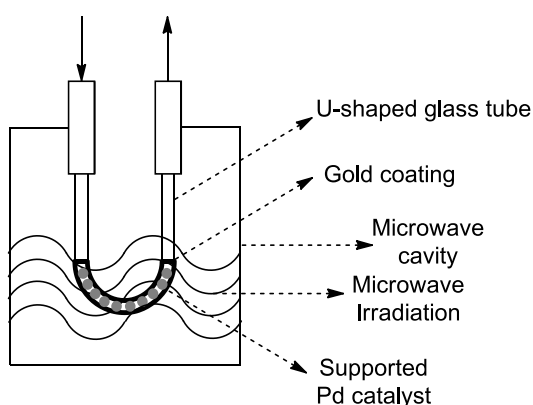


**Figure 5.11** Typical microreactor setup using both a coil and packed column configuration.

can be heated or cooled as required and run in either series or parallel for sequential or divergent synthetic pathways. An example of a typical reactor setup using both a coil and a packed column is shown in Figure 5.11. Residence time (the total amount of time a molecule stays within the reaction area) can vary with both flow rate and reaction volume. The nature of these systems also allows access to novel extremes of temperature and pressure, not accessible when utilising conventional apparatus. There are also intrinsic safety benefits with carrying out reactions under flow conditions as highly toxic, hazardous and explosive intermediates can be synthesised in limited quantities and used in situ, thus minimising exposure.

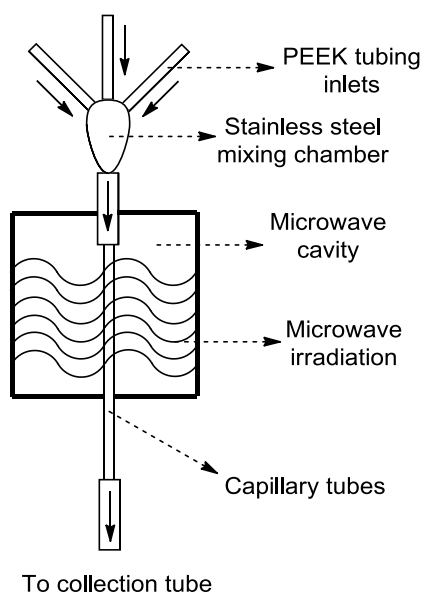
#### 5.4.2 Microwave Assisted Continuous Flow Organic Synthesis

Microwave assisted organic synthesis (MAOS) in batch reactions can dramatically reduce reaction times for coupling reactions.<sup>167</sup> Due to the 'superheated' high temperatures and pressures that can be achieved, the reaction conditions have been shown to be analogous to those present in continuous flow systems and as such microwave batch protocols can serve to predict how different cross-coupling conditions will behave in flow.<sup>122</sup> In addition to this, microwave assisted continuous flow organic synthesis (MACOS) has shown that combining the benefits of microwave heating and continuous flow processing can provide additional reaction control.<sup>100</sup> Haswell et al. conducted Suzuki couplings in a 'U-shape' glass tube of which the external surface was coated in a thin film of gold.<sup>168</sup> The tube was filled with an alumina supported Pd catalyst and mounted inside a standard bench top laboratory microwave (Figure 5.12) and irradiated continuously at a power of 90-150 W.



**Figure 5.12** Gold-coated U-shaped glass tube for microwave assisted Suzuki coupling in flow.

The gold coating facilitated efficient microwave absorption and subsequent heating of the reaction area and was shown to give good conversions for the Suzuki coupling of a variety of aryl halides with phenylboronic acid, using  $\text{K}_2\text{CO}_3$  as a base and DMF/ $\text{H}_2\text{O}$  as mixed solvent, in a residence time of 60 s. Ley et al. have demonstrated the use of Pd EnCat<sup>TM</sup> in a MACOS set up for high throughput synthesis of compound libraries via Suzuki coupling of a boronic acid and aryl halide in the presence of tetrabutylammonium base in ethanol.<sup>105</sup> To avoid catalyst degradation a cycle of heating for 30 s at 50 W followed by cooling for 18 s was used, along with a flow rate of 0.1 mL/min (65 s residence time within the microwave chamber) and an Amberlyst 15 scavenger column to remove the base and boron-containing by-products. Around the same time Organ et al. prepared a capillary coated with a thin film of palladium and described its use as a catalyst for both Suzuki and Heck couplings in conjunction with microwave heating (Figure 5.13).<sup>169</sup>



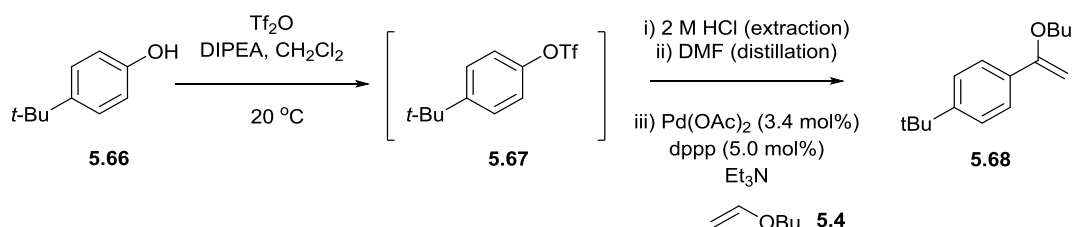
**Figure 5.13** Capillary coated with a Pd film for microwave assisted continuous flow cross-couplings.

The palladium film was prepared by filling a capillary 1150 mm thick with a 0.1 mmol/mL solution of  $\text{Pd}(\text{OAc})_2$  and heating at 150 °C for 30 min, which resulted in a porous film of Pd crystallites that were 60-140 nm in diameter. This system was shown to give excellent conversions for both Suzuki and Heck couplings of electron rich and electron deficient

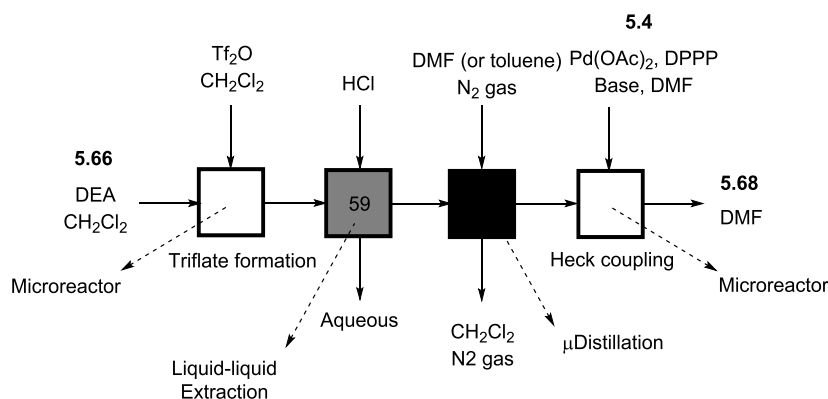
functionalities with a flow rate of 10  $\mu\text{L}/\text{min}$ , although no specific residence times were reported. When identical conditions were subjected to conventional heating, conversion was just over half that obtained previously showing that microwave irradiation gave added benefits other than simply heating the Pd film. During prolonged heating of the capillary, Pd leaching from the film was measured to be  $<2$  ppm, suggesting that coupling was occurring at the metal surface. However, Pd residues in the product mixtures were found to be higher (19.2 ppm) showing that soluble Pd species were being generated during the reaction. It was postulated that oxidative addition of the aryl halide could be occurring at the surface of the film, liberating atomic Pd, before transmetallation and reductive elimination take place in solution away from the surface.

#### **5.4.3 Towards sequential coupling reactions in flow**

The ability to perform several synthetic reaction steps in sequence has long been seen as an ultimate goal in continuous flow processing.<sup>102</sup> However, the use of vastly different solvents specific to each reaction and large excesses of reagents are significant barriers to achieving this goal. One technological solution is to use in-line separation processes to change solvents or remove unused/unwanted reagents prior to the next reaction step. Building on previous work on in-line continuous separation processes on the micro-scale,<sup>170-172</sup> Jensen and Buchwald showcased the use of in-line liquid-liquid extraction and distillation processes in the production of an butyl vinyl ether **61** via Heck coupling of an aryl triflate **59** and an alkene **60** (Scheme 5.23).<sup>173</sup> The first step involved the preparation of the aryl triflate from a phenol derivative **58** and triflic anhydride in the presence of a stoichiometric base, with dichloromethane as the solvent of choice. This was then followed by extraction with 2 M aqueous HCl to remove the base and unwanted triethylammonium salts and exchange of the lower boiling dichloromethane with higher boiling DMF via distillation (Figure 5.14). The resulting effluent consisting of the triflate in DMF was then fed into a microreactor to afford the required Heck coupling products in excellent yields. They have also utilised this methodology for the subsequent Suzuki coupling of aryl triflates.<sup>174</sup>



**Scheme 5.23** Sequential formation of an aryl triflate **5.67** and subsequent Heck coupling in flow.



**Figure 5.14** Sequential reaction, microextraction, microdistillation, cross-coupling in flow

## 5.5 Summary

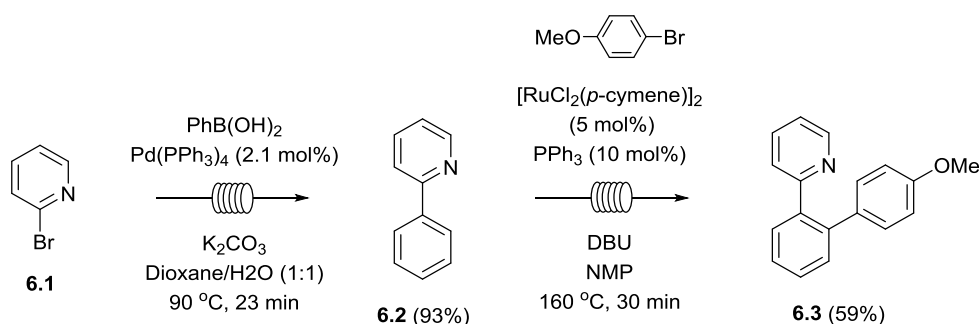
Palladium catalysed cross-couplings in continuous flow systems present a number of opportunities for synthesis with respect to speed, efficiency, safety, ease of scale up and access to novel temperature and pressure conditions, in comparison to conventional batch based synthesis. A wide selection of both homogeneous and heterogeneous catalytic systems are available for use in flow systems on a laboratory scale, and each has its own merits and disadvantages with respect to separation, activity, leaching, mixing and scale-up, dependant on application. There have been significant technological advances in recent years with respect to more efficient, scaleable processing methods, particularly microwave assisted synthesis for which continuous processing is key to its implementation in industrial operations. Separation processes too have come a long way in helping to realise the goal of performing sequential reactions in flow. A widely held criticism of microreactor flow synthesis is its current inability to handle slurries and precipitation of reactants, which can cause blockages and inhibit mixing. The use of

ultrasonic irradiation has been shown to improve this; however, significant developments are still required for Pd catalysed cross-couplings to become routine in continuous flow synthesis. Overall, continuous flow systems hold significant promise for cross-couplings in the future and their use will only continue to grow, driven by the search for faster, safer, more efficient and scaleable processing methodologies.

## 6. Sequential C-X and C-H bond Functionalisations in Flow

This chapter deals with work on the development of a sequential cross-coupling/C-H functionalisation protocol in flow. As discussed in Chapter 5, continuous-flow systems offer several advantages over batch processes, particularly with respect to the speed and efficiency of reactions, and as such cross-couplings in flow have been widely studied. Direct C-H functionalisations tend to be carried out under similar, albeit more extreme, reaction conditions to cross-couplings in batch operation, so it was logical to assume the same trend may apply to flow.

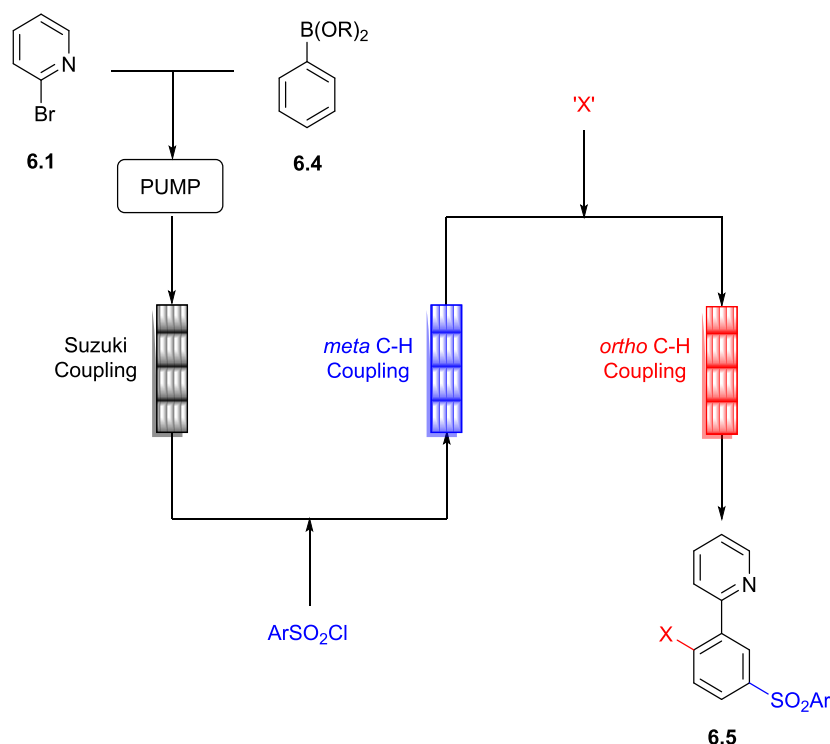
Up until very recently, there were no examples of direct C-H functionalisation reactions conducted in flow in the literature. The first such example, reported earlier this year by Schnürch and co-workers, entailed a Ru-catalysed arylation of 2-phenylpyridine derivatives.<sup>175</sup> By coincidence this work also happened to be part of a sequential strategy, involving a Pd-catalysed cross-coupling to form the 2-phenylpyridines prior to the C-H functionalisation step (Scheme 6.1).



**Scheme 6.1** Sequential cross-coupling/*ortho* arylation in flow

### 6.1 Blueprint for a Sequential Flow Protocol

The original premise for our sequential strategy was similar to that devised by Schnürch, entailing a Suzuki coupling followed by direct C-H functionalisation of the resulting 2-arylpyridine intermediate. As promising results had been obtained with sequential regioselective C-H functionalisations in batch (see Chapter 3), it was thought that the introduction of a second C-H functionalisation step may also be possible if the right



**Scheme 6.2** Sequential cross-coupling/C-H functionalisation strategy

combination of reaction conditions could be found. Scheme 6.2 shows an example of what such a sequence could look like, using the sequential *meta* then *ortho* batch protocol discussed in section 3.3, to access a highly functionalised benzene derivative such as **6.5**.

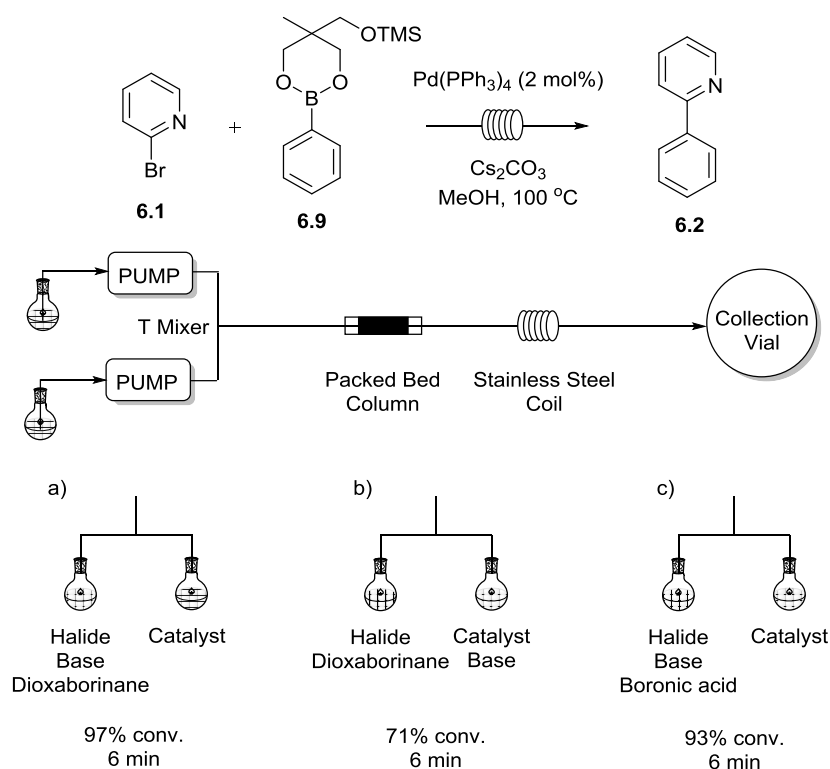
## 6.2 Cross-couplings in Flow

Previous work within the Frost group concerning cross-couplings in flow centred on the development of a robust and reusable supported Pd catalyst.<sup>132</sup> The catalyst **6.7** comprised a spherical core of amorphous silica upon which Pd nanoparticles were supported, before encapsulation within a porous polystyrene coating (Scheme 6.3). Catalyst **6.7** was shown to be robust with minimal catalyst degradation or leaching of Pd ensuring it could be used for extended periods of time. However, the downside was that the catalyst did not display particularly good activity for cross-couplings, with only aryl iodides giving good yields and even then relatively long residence times were necessary. The coupling of 2-bromopyridine **6.1** and benzenboronic acid **6.8** with this catalyst only proceeded to furnish 46% of the required substrate **6.2**. As this is the key intermediate in





The catalyst and reagent solutions were assigned to different pumps and introduced into the reactor via a T-mixer. An additional packed bed column was also used to ensure efficient mixing of the two solutions.<sup>104</sup> Using this reactor setup shown in Scheme 6.4a a range of flow rates were used from 1-5 mL/min, corresponding to residence times between 2-12 min. The optimum residence time was found to be 6 min, which gave a conversion of 97% to the required 2-phenylpyridine **6.2**. An integral part of the mechanism is the hydrolysis of the dioxaborinane to the corresponding boronic acid in situ, mediated by the base, from which coupling occurs. As the dioxaborinane and base were pre-mixed it was possible that hydrolysis could be occurring prior to the reagents entering the reaction environment, effectively negating the need for the boronic ester. To test this, the second run was conducted with the base added to the catalyst solution instead of the reagent solution, to prevent hydrolysis occurring before the two solutions are mixed (Scheme 6.4b). This led to a substantial drop in conversion to 71%, with the same residence time of 6 min, indicating that hydrolysis was indeed occurring prior to entering the reactor. Further evidence of this was obtained in the third run, where the dioxaborinane was replaced with the boronic acid (Scheme 6.4c). A conversion of 93% to



**Scheme 6.4** Suzuki coupling with dioxaborinanes in flow

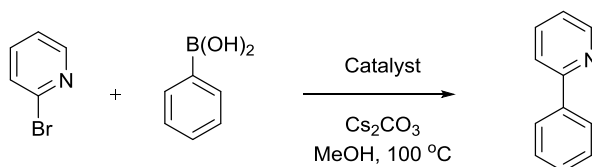
2-phenylpyridine **6.2** was observed, mirroring that seen in first run with the pre-mixed dioxaborinane.

An explanation for this, at first surprising result, lies in the inherent advantages associated with continuous-flow processing. The reason the dioxaborinanes work so well in batch operation is due to the controlled release of boronic acid over time, via hydrolysis of the ester. This limits the amount of time the boronic acid is present in the reaction environment and prevents decomposition and byproduct formation. It is this same advantage that is inherent in continuous-flow processes. Because of the much smaller reactor volumes used, the reagents are continuously pumped through the reactor and only spend a fraction of the total time in the reaction environment. This has the same effect of limiting unwanted side reactions in cross-couplings as using a boronic ester.

### 6.2.2 Boronic acids in flow

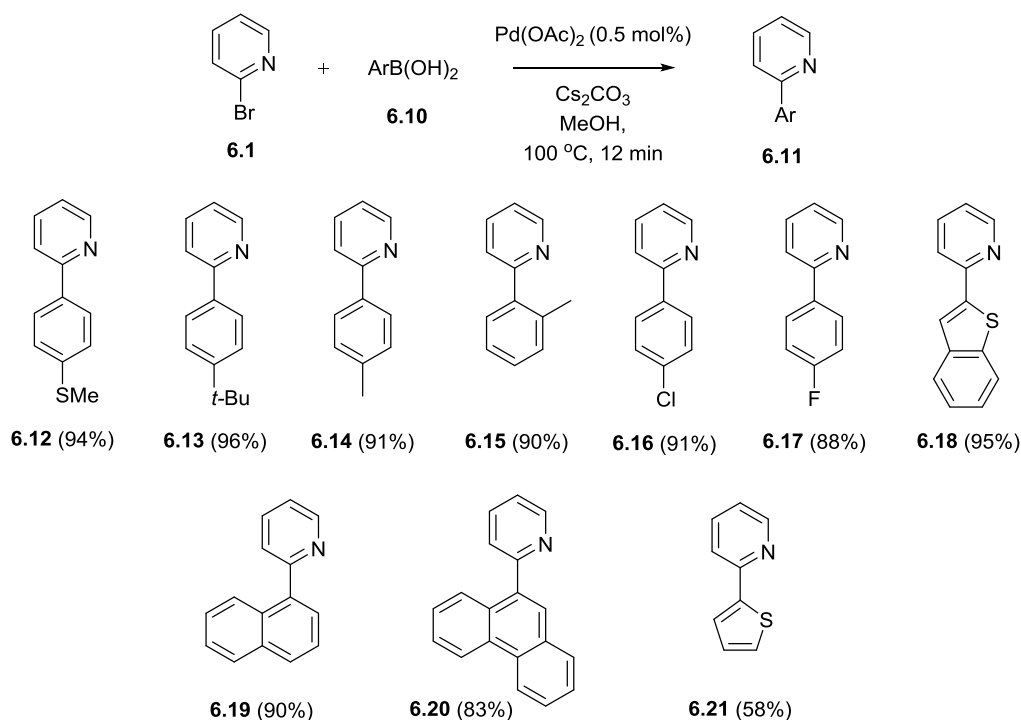
Upon further optimisation of the reaction conditions it was found that Pd(OAc)<sub>2</sub> was a far more active catalyst than Pd(PPh<sub>3</sub>)<sub>4</sub>, enabling the catalyst loading to be reduced to 0.5

**Table 6.1** Optimisation of Suzuki coupling with benzeneboronic acid



| Entry | Catalyst                           | Catalyst Loading (mol%) | Boronic acid equivalents | Residence time (min) | Conversion (%) <sup>[a]</sup> |
|-------|------------------------------------|-------------------------|--------------------------|----------------------|-------------------------------|
| 1     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | 2                       | 1.5                      | 6                    | 93                            |
| 2     | Pd(OAc) <sub>2</sub>               | 2                       | 1.5                      | 2                    | 97                            |
| 3     | Pd(OAc) <sub>2</sub>               | 1                       | 1.5                      | 2                    | 95                            |
| 4     | Pd(OAc) <sub>2</sub>               | 0.5                     | 1.5                      | 2                    | 98                            |
| 5     | Pd(OAc) <sub>2</sub>               | 0.5                     | 1.05                     | 2                    | 95 (93) <sup>[b]</sup>        |
| 6     | Pd/C                               | -                       | 1.5                      | 20                   | 26                            |
| 7     | Pd EnCat                           | -                       | 1.5                      | 20                   | 31                            |
| 8     | Catalyst <b>6.7</b>                | -                       | 1.5                      | 20                   | 12                            |

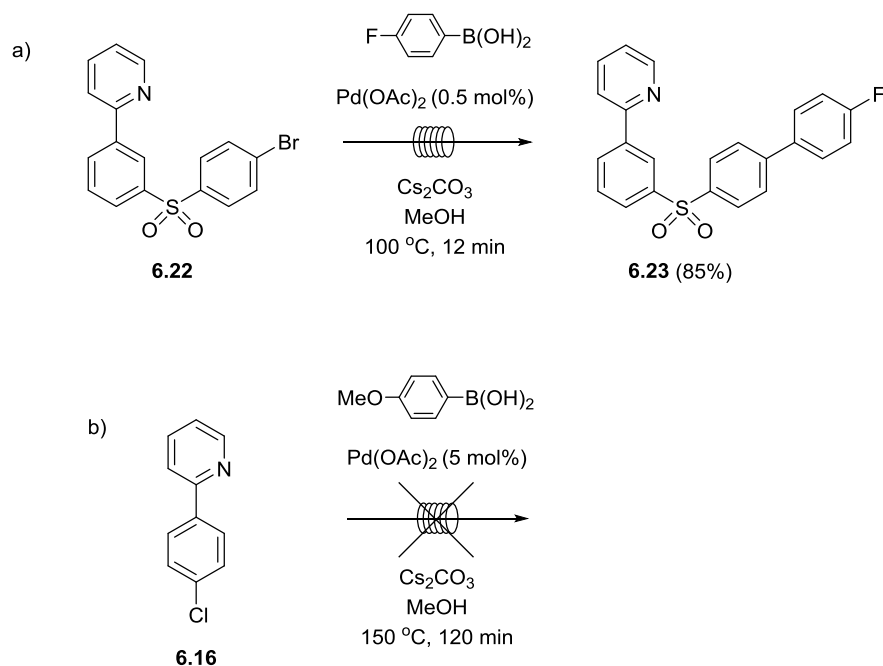
[a] Calculated from <sup>1</sup>H NMR spectra. [b] Isolated yield.



**Scheme 6.5** Scope of  $\text{Pd}(\text{OAc})_2$ -catalysed Suzuki coupling in flow

mol% and the residence time lowered to 2 min, with no appreciable decrease in conversion. Due to the afore mentioned ability of flow to minimise boronic acid decomposition and side reactions, the equivalents of boronic acid could be also be lowered to just 1.05 equivalents whilst maintaining excellent conversion. These optimised conditions were then used to synthesise several 2-arylpyridine analogues, all in excellent yield, with the exception of thiophene derivative **6.21** which is known to be a particularly difficult example to synthesise. Suzuki coupling of *p*-brominated sulfone **6.22** with 4-fluorobenzeneboronic acid also proceeded readily to afford another example of a polyaryl sulfone to compliment those discussed in Chapter 3 (Scheme 6.6a).

To date sequential Suzuki couplings have not been demonstrated in flow, so an attempt was made to perform a second coupling of *p*-chloro analogue **6.16** with 4-methoxybenzeneboronic acid, in order to determine whether it could be a viable option for the synthesis of extended aromatic compounds. However, even after extended residence times and significant increases in reaction temperature and catalyst loading, no coupling was observed, and only starting material returned (Scheme 6.6b)



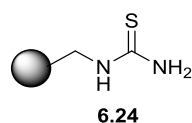
**Scheme 6.6** Suzuki coupling of brominated sulfone and *p*-Cl 2-phenylpyridine

### 6.2.3 ICP-MS leaching studies

One of the biggest drivers for the development of heterogeneous and supported catalysts is their ease of separation from the reaction products. However, heterogeneous catalysts often display lower catalytic activities due to the need for the reactants to cross the phase boundary and adsorb onto the catalyst surface, where the reaction occurs. Many of the common Pd catalysts also exhibit significant amounts of leaching and subsequent loss of activity, as discussed in more detail in Chapter 5. This is a particular problem in the pharmaceutical industry where strict limits are imposed on trace metal concentrations in their products. Therefore, the choice between using a homogeneous or heterogeneous catalyst for reactions in a flow system is not always straightforward.

Despite the obvious benefits of higher catalytic activities and shorter reaction times, in order to justify the use of a homogeneous Pd catalyst, post-reaction separation of the residual palladium must be considered. There are several reports exemplifying the use of biphasic solvent systems to facilitate catalyst separation, but by far the simplest option is to employ a scavenger reagent. These are commercially available and – in the case of continuous processes – can be used in a packed bed and fitted as an end-of-pipe solution.

In an effort to determine the viability of this homogeneous Pd(OAc)<sub>2</sub>-catalysed cross-coupling methodology to be used as part of a sequential protocol, ICP-MS analysis was used to measure residual Pd content. The post-reaction products, both before and after the use of a scavenger, were analysed along with several other heterogeneous Pd catalysts in order to make a direct comparison. The scavenger chosen for use in this experiment was QuadraPure TU; a commercially available metal scavenger consisting of thiourea supported on silica (Scheme 6.7).



**Scheme 6.7** QuadraPure TU metal scavenger

**Table 6.2** ICP-MS measurements of residual palladium content

| Entry | Catalyst                                | Pd content (mg/L) |
|-------|---|-------------------|
| 1     | Pd(OAc) <sub>2</sub> (before scavenger) | 3720              |
| 2     | Pd(OAc) <sub>2</sub> (after scavenger)  | 20                |
| 3     | Pd/C                                    | 6                 |
| 4     | Pd EnCat                                | 31                |
| 5     | Catalyst <b>6.7</b>                     | 2                 |

From Table 6.2 it can be seen that the use of a scavenger facilitates removal of 99.5% of the residual palladium present in the homogeneously-catalysed reaction. More importantly, the palladium content of the post-scavenger sample is of the same order of magnitude as those of the heterogeneous catalysts. Moreover, the amount of Pd leaching reported in the literature for Pd/C and Pd EnCat, under optimised reaction conditions, is significantly higher than these values.

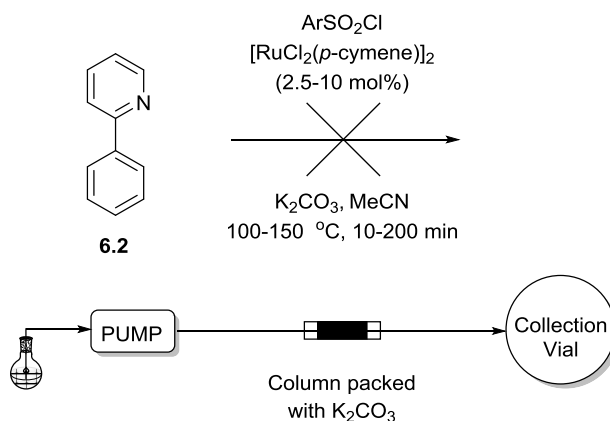
With all of this data in hand it was decided that this homogeneous Pd(OAc)<sub>2</sub>-catalysed Suzuki coupling methodology was the best candidate to take forward as part of the sequential strategy.

### 6.3 C-H Functionalisation in Flow

For the second step in the sequential flow process, attention was turned to the several of C-H functionalisation protocols previously used as part of sequential protocols in batch, namely; *meta* sulfonation, *ortho* hydroxylation and oxidative homocoupling. The starting point for the investigation of these protocols in flow was the optimised conditions used in batch operation for each method.

#### 6.3.1 *meta* sulfonation

The first consideration for conducting the *meta* sulfonation in flow was the use of the inorganic base  $K_2CO_3$ , which is largely insoluble in the reaction solvent MeCN. The usual approach to solving this problem would be to use a biphasic aqueous/organic solvent system or perhaps, as found with optimisation of the Suzuki couplings in flow, substituting the  $K_2CO_3$  for a more soluble base. However, in this case neither of these options were available. The use of any protic solvents would only serve to hydrolyse the sulfonyl chloride to the sulfonic acid and sabotage the reaction. This would also be the case if any amine bases were used and other inorganic bases such as carbonates or acetates that might work were not soluble in the desired solvents. This only left one option for a flow process, which was to use a column packed with the base as the reaction chamber, through which the other reagents could be pumped (Scheme 6.8). A range of temperatures, residence times and catalyst loadings were investigated but no reaction products were observed with only starting material returned.

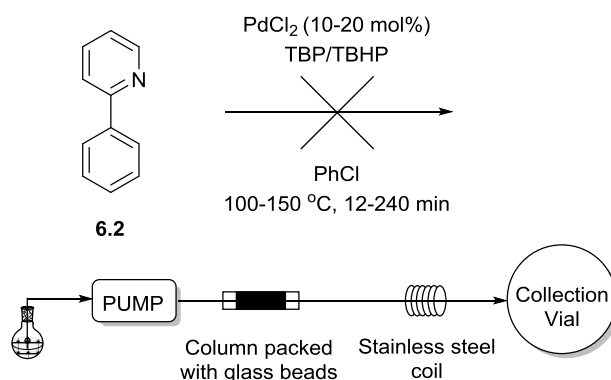


**Scheme 6.8** Reaction setup used for *meta* sulfonation in flow

This result is not particularly surprising due to the narrow set of operational conditions that are needed in batch operation to obtain any products. The necessity of having to pack the base into a column could also hinder the reaction as this is only usually done with supported catalysts and is not common with bases.

### 6.3.2 Hydroxylation

Unlike the *meta* sulfonation methodology, the reagents for the *ortho* hydroxylation protocol were all soluble in the reaction solvent PhCl and gave a homogeneous reaction solution. This made it significantly easier to devise a method for conducting this transformation in flow than for the previous example, as a stainless steel coil could be used as the reactor. A column packed with glass beads was also included to ensure that the reagents were well mixed prior to entering the coil. Again a range of temperatures, residence times and catalyst loadings were investigated and the oxidant was also varied to see if this could have an impact on the results. Unfortunately, as with the *meta* sulfonation, no reaction products were observed and only starting material was returned in each case.



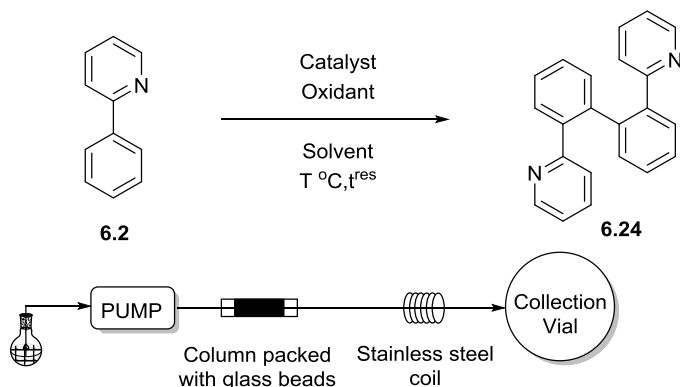
**Scheme 6.9** Reaction setup used for *ortho* hydroxylation in flow

### 6.3.3 Oxidative homocoupling

The frequency with which byproducts, derived from oxidative homocoupling processes of 2-phenylpyridines, were obtained during the work described in Chapters 2 and 3, suggested that they could be more facile targets for demonstration in flow. There are



three reported methods for the dimerisation of 2-arylpyridines which are discussed in more detail in Chapter 4, each using a different transitional metal and oxidant combination. The reaction setup was the same as the one used for the hydroxylation with



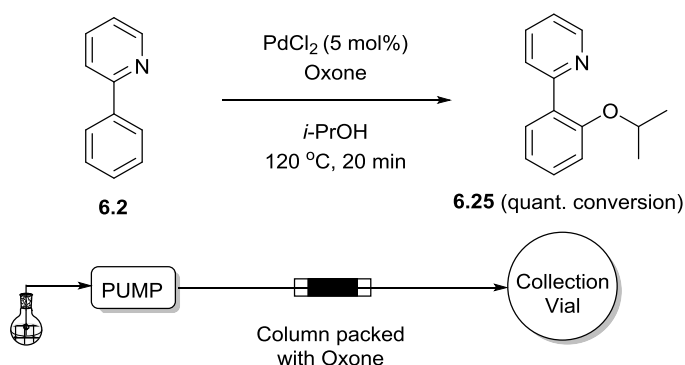
**Scheme 6.10** Reaction setup used for oxidative homocoupling in flow

**Table 6.3** Experimental conditions for oxidative homocoupling in flow

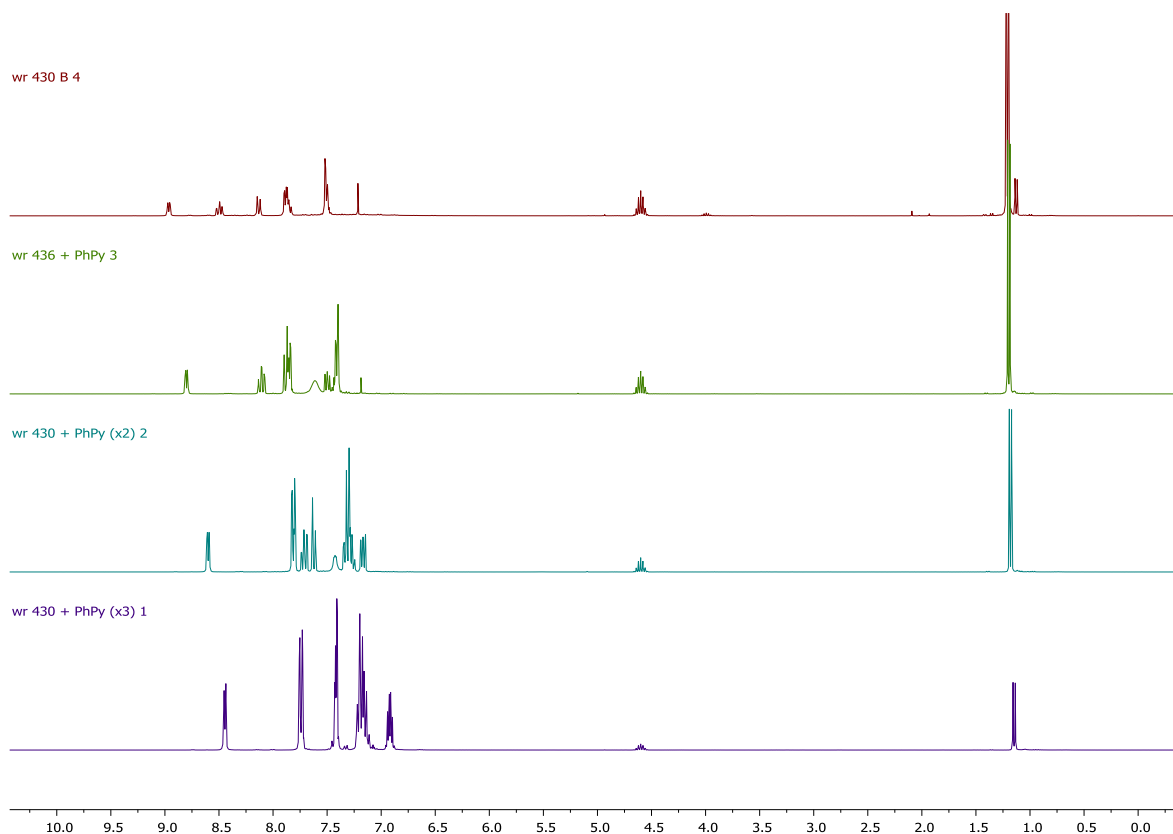
| Entry            | Catalyst   | Oxidant                         | Solvent        | Temp.<br>(°C) | Res. Time<br>(min) | Conversion<br>(%) <sup>[c]</sup> |
|------------------|--|---------------------------------|----------------|---------------|--------------------|----------------------------------|
| 1                | [RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub><br>(2.5 mol%) | TBHP<br>(2 mmol)                | PhCl           | 150           | 200                | 0                                |
| 2                | [RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub><br>(2.5 mol%) | FeCl <sub>3</sub><br>(0.8 mmol) | PhCl           | 150           | 200                | 10                               |
| 3                | Cu(OAc) <sub>2</sub><br>(1 equiv)                                  | I <sub>2</sub><br>(2 mmol)      | MeCN           | 150           | 200                | 12                               |
| 4 <sup>[a]</sup> | Copper coil  | I <sub>2</sub><br>(2 mmol)      | MeCN           | 150           | 200                | 6                                |
| 5 <sup>[b]</sup> | Pd(OAc) <sub>2</sub><br>(5 mol%)                                   | Oxone<br>(Excess)               | <i>i</i> -PrOH | 150           | 20                 | 15 <sup>[d]</sup>                |
| 6 <sup>[b]</sup> | PdCl <sub>2</sub><br>(5 mol%)                                      | Oxone<br>(Excess)               | <i>i</i> -PrOH | 120           | 20                 | 0 <sup>[d]</sup>                 |

[a] A copper reaction coil with a volume of 10 mL was used in place of stainless steel. [b] Oxone was packed into the omnifit reaction column in place of glass beads. [c] Calculated from <sup>1</sup>H NMR spectrum. [d] Alkoxylation product **6.25** was the major product from this reaction.

both packed column and coil reactors. A summary of the results is shown in Table 6.3. Small amounts of the dimeric products were obtained for each method at 150 °C in a residence time of 200 min. 150 °C is the upper temperature limit of the vapourtec R-Series microreactor, so it was not possible to raise it any further and a residence time of 200 min is already undesirable so no effort was made to increase it further. Interestingly, under the Pd(OAc)<sub>2</sub>-catalysed conditions significant amounts of another product, believed to be alkoxide **6.25** were observed. This was optimised to favour alkoxide formation and



**Scheme 6.11** Reaction setup used for alkoxylation in flow



**Figure 6.1** Stacked <sup>1</sup>H NMR spectra of **6.25** before and after spiking with 2-PhPy

quantitative conversion to **6.25** was obtained. However when attempts were made to isolate this compound by flash column chromatography it decomposed back to 2-phenylpyridine. Recrystallisation from the reaction solution was also tried to no avail. *ortho* alkoxyated 2-phenylpyridine derivatives are not known to decompose easily so it was strange that this was observed. To shed light why this was happening several  $^1\text{H}$  NMR experiments were run, each one spiked with varying amounts of the starting material 2-phenylpyridine (Figure 6.1). From this it was seen that as the amount of 2-phenylpyridine was increased, instead of additional peaks corresponding to 2-phenylpyridine appearing in the spectrum, the existing peaks started to shift to eventually resemble 2-phenylpyridine itself. This surprising result suggests that the basicity of 2-phenylpyridine was causing the compound to decompose, like it was seen to do when eluted through a silica column. This is also not indicative of *ortho*-alkoxyated 2-phenylpyridines and so it was unlikely that the observed product was alkoxide **6.25**, and instead was believed to be a salt of 2-phenylpyridine which was unstable to acidic and basic conditions, although no such compound could be isolated from the reaction mixture.

## 6.4 Conclusions

In conclusion, a fast, efficient homogeneous-catalysed cross-coupling methodology has been developed for coupling 2-bromopyridine with a variety of boronic acids in continuous-flow operation. The protocol utilises  $\text{Pd}(\text{OAc})_2$  as the catalyst in a low loading of 0.5 mol% to give excellent yields within 2-12 min residence time. Using a commercially available scavenging reagent, the levels of residual palladium detected in the products was of the same order of magnitude as reactions run with several heterogeneous Pd catalyst systems. Following this, focus then turned to the development of continuous-flow methods for catalytic C-H functionalisation processes. Two out of the three protocols investigated gave no reaction products at all, even with high temperatures and long residence times. Oxidative homocoupling of 2-phenylpyridines showed small amounts of dimeric products that could not be improved further. The homocoupling protocol catalysed by  $\text{PdCl}_2$  gave quantitative conversion to a compound believed to be a salt of 2-phenylpyridine, but this could not be isolated so its structure remains elusive.

## 7. Experimental

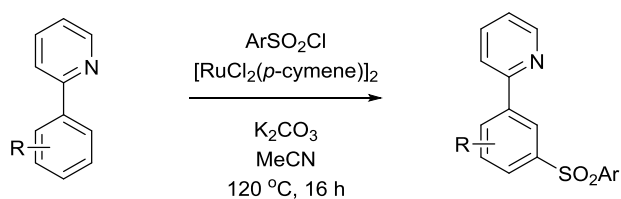
### 7.1 Compound Index

| Compound    | Page      | Compound    | Page      |
|-------------|-----------|-------------|-----------|
| <b>2.31</b> | 137       | <b>4.2</b>  | 170       |
| <b>2.32</b> | 131       | <b>4.14</b> | 158       |
| <b>2.33</b> | 138       | <b>4.15</b> | 159       |
|             |           | <b>4.16</b> | 159       |
|             |           | <b>4.17</b> | 160       |
| <b>3.3</b>  | 124       | <b>4.18</b> | 160       |
| <b>3.8</b>  | 150       | <b>4.19</b> | 161       |
| <b>3.9</b>  | 150       | <b>4.20</b> | 161       |
| <b>3.10</b> | 151       | <b>4.21</b> | 162       |
| <b>3.11</b> | 151       | <b>4.22</b> | 162       |
| <b>3.12</b> | 140       | <b>4.23</b> | 165       |
| <b>3.13</b> | 140       | <b>4.24</b> | 163       |
| <b>3.14</b> | 133       | <b>4.25</b> | 163       |
| <b>3.15</b> | 135       | <b>4.26</b> | 164       |
| <b>3.16</b> | 136       | <b>4.27</b> | 171       |
| <b>3.17</b> | 134 & 154 | <b>4.28</b> | 172       |
| <b>3.21</b> | 125       | <b>4.29</b> | 173       |
| <b>3.22</b> | 126       | <b>4.30</b> | 174       |
| <b>3.23</b> | 127       | <b>4.31</b> | 175       |
| <b>3.24</b> | 128       | <b>4.32</b> | 176       |
| <b>3.25</b> | 129       | <b>4.33</b> | 177       |
| <b>3.26</b> | 130       | <b>4.34</b> | 178       |
| <b>3.27</b> | 131       | <b>4.37</b> | 179       |
| <b>3.28</b> | 132       |             |           |
| <b>3.29</b> | 141       | <b>6.2</b>  | 181       |
| <b>3.30</b> | 152       | <b>6.12</b> | 181       |
| <b>3.31</b> | 153       | <b>6.13</b> | 182       |
| <b>3.32</b> | 155       | <b>6.14</b> | 182       |
| <b>3.33</b> | 168       | <b>6.15</b> | 183       |
| <b>3.34</b> | 169       | <b>6.16</b> | 183       |
| <b>3.36</b> | 142       | <b>6.17</b> | 184       |
| <b>3.37</b> | 143       | <b>6.18</b> | 184       |
| <b>3.38</b> | 144       | <b>6.19</b> | 185       |
| <b>3.39</b> | 145       | <b>6.20</b> | 185       |
| <b>3.40</b> | 146       | <b>6.21</b> | 186       |
| <b>3.41</b> | 147       | <b>6.23</b> | 187       |
| <b>3.42</b> | 148       | <b>6.24</b> | 188 & 189 |
| <b>3.43</b> | 149       |             |           |
| <b>3.45</b> | 166       |             |           |

## 7.2 General Considerations

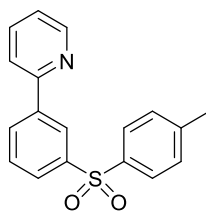
Unless otherwise noted, all reagents and catalysts were commercially available and purchased from Sigma-Aldrich Company Ltd and were used without further purification. Silica gel plates (GF<sub>254</sub>) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. Dried solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. The <sup>1</sup>H NMR spectra were recorded on Bruker Avance 250, 300, 400 and 500 instruments and <sup>13</sup>C NMR spectra were recorded on Bruker Avance 300 and 400 instruments, all with TMS as the internal standard. The mass spectra were run on a microTOF electrospray time of flight (ESI-TOF) coupled to an Agilent 1200 LC system (University of Bath). IR spectra were recorded on Perkin-Elmer 1600 FT IR spectrometer with only selected absorbance quoted as  $\nu$  in cm<sup>-1</sup>. All capillary melting points were recorded using a Bibby Scientific melting point apparatus Stuart SMP10 digital. Continuous flow experiments were conducted using a Vapourtec R-Series instrument fitted with 6.6 mm x 100 mm Omnifit columns and /or stainless steel and copper coils with a volume of 10 mL.

### 7.3 General procedure for the preparation of *meta*-sulfonated 2-arylpyridines



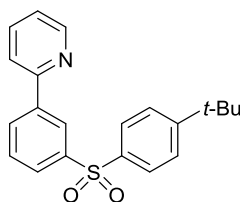
2-arylpyridine (2.0 mmol), sulfonyl chloride (6.0 mmol), potassium carbonate (4.0 mmol, 0.55 g)  $[\text{RuCl}_2(p\text{-cymene})]_2$  (0.05 mmol, 30.6 mg) and acetonitrile (5.0 mL) were added to a nitrogen-purged carousel tube, sealed with a Teflon cap and heated to  $120\text{ }^\circ\text{C}$  with stirring for 15 h. After cooling to room temperature, the reaction mixture was washed with brine (20 mL), extracted with dichloromethane (3 x 20 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel.

### 7.3.1 2-(3-Tosylphenyl)pyridine (3.3)



2-Phenylpyridine (2.0 mmol, 0.310 g) and tosyl chloride (6 mmol, 1.134 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (43% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.62 (dt,  $J = 4.8, 1.5$  Hz, 1H), 8.47 (t,  $J = 1.7$  Hz, 1H), 8.14 (ddd,  $J = 7.8, 1.7, 1.2$  Hz, 1H), 7.88 (ddd,  $J = 7.8, 1.8, 1.1$  Hz, 1H), 7.79 (d,  $J = 8.3$  Hz, 2H), 7.74 – 7.63 (m, 2H), 7.51 (t,  $J = 7.8$  Hz, 1H), 7.26 – 7.14 (m, 3H), 2.30 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.4, 150.0, 144.3, 142.7, 140.8, 138.7, 137.1, 131.4, 130.0, 129.8, 127.8, 125.9, 123.1, 120.8, 21.6. Data in accordance with literature values.<sup>31</sup>

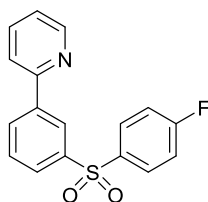
### 7.3.2 2-((3-((4-*tert*-Butylphenyl)sulfonyl)phenyl)pyridine (3.21)



2-Phenylpyridine (2.0 mmol, 0.310 g) and 4-*tert*-butylphenylsulfonyl chloride (6 mmol, 1.392 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (26% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.62 (d, *J* = 4.5 Hz, 1H), 8.49 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.71 (q, *J* = 7.4, 6.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.15 (m, 1H), 1.21 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.2, 155.2, 149.8, 142.6, 140.5, 138.5, 137.3, 131.5, 129.8, 128.0, 127.6, 126.4, 126.0, 123.1, 120.9, 35.2, 31.1. Data in accordance with literature values.<sup>31</sup>

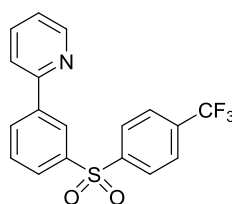


### 7.3.3 2-(3-((4-Fluorophenyl)sulfonyl)phenyl)pyridine (3.22)



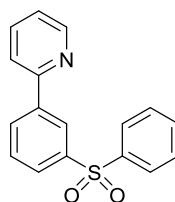
2-Phenylpyridine (2.0 mmol, 0.310 g) and 4-fluorophenylsulfonyl chloride (6 mmol, 1.158 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (40% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.61 (d, *J* = 4.7 Hz, 1H), 8.49 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.89 – 7.84 (m, 1H), 7.68 (dd, *J* = 6.5, 1.5 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 6.6, 4.5, 2.1 Hz, 1H), 7.08 (t, *J* = 8.5 Hz, 2H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 165.5 (d, *J* = 256.0 Hz), 155.1, 150.0, 142.1, 140.9, 137.6 (d, *J* = 3.2 Hz), 137.1, 131.7, 130.6 (d, *J* = 9.6 Hz), 129.9, 127.8, 125.9, 123.1, 120.7, 116.7 (d, *J* = 22.7 Hz). Data in accordance with literature values.<sup>31</sup>

#### 7.3.4 2-((3-((4-Trifluoromethylphenyl)sulfonyl)phenyl)pyridine (3.23)



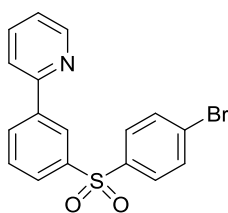
2-Phenylpyridine (2.0 mmol, 0.310 g) and 4-trifluoromethylphenylsulfonyl chloride (6 mmol, 1.464 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (17% yield). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.69 (dd, *J* = 3.5, 2.3 Hz, 1H), 8.60 (t, *J* = 1.7 Hz, 1H), 8.25 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 8.02 – 7.94 (m, 1H), 7.83 – 7.71 (m, 4H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.29 (ddd, *J* = 6.7, 4.9, 2.1 Hz, 1H). <sup>13</sup>C NMR δ 154.9, 149.9, 145.1, 141.1 (d, *J* = 10.9 Hz), 137.1, 134.8 (q, *J* = 33.1 Hz), 132.0, 130.0, 128.8, 128.2, 128.0, 127.0, 126.5 (q, *J* = 3.7 Hz), 126.2, 124.9, 123.2, 121.2, 120.7. Data in accordance with literature values.<sup>31</sup>

### 7.3.5 2-(3-(Benzenesulfonyl)phenyl)pyridine (3.24)



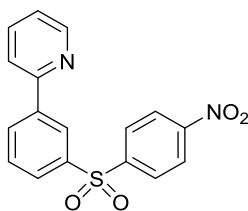
2-Phenylpyridine (2.0 mmol, 0.310 g) and benzenesulfonyl chloride (6 mmol, 1.056 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (38% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.67 (d, *J* = 4.7 Hz, 1H), 8.57 (t, *J* = 1.7 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.02 – 7.91 (m, 3H), 7.80 – 7.69 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.54 – 7.43 (m, 3H), 7.25 (ddd, *J* = 6.2, 4.7, 2.4 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.2, 149.9, 142.2, 141.5, 140.8, 137.1, 133.3, 131.5, 129.8, 129.3, 127.9, 127.7, 126.0, 123.1, 120.7. Data in accordance with literature values.<sup>31</sup>

### 7.3.6 2-(3-((4-Bromophenyl)sulfonyl)phenyl)pyridine (3.25)



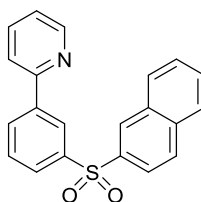
2-Phenylpyridine (2.0 mmol, 0.310 g) and 4-bromophenylsulfonyl chloride (6 mmol, 1.518) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (48% yield). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.62 (d, *J* = 4.9 Hz, 1H), 8.48 (s, 1H), 8.15 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.87 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.76 (dt, *J* = 9.1, 2.2 Hz, 2H), 7.74 – 7.63 (m, 2H), 7.59 – 7.47 (m, 3H), 7.20 (ddd, *J* = 6.6, 4.8, 1.9 Hz, 1H). <sup>13</sup>C NMR δ 155.3, 150.2, 142.0, 141.2, 140.8, 137.3, 132.9, 132.0, 130.1, 129.5, 128.8, 128.1, 126.2, 123.4, 120.9. Data in accordance with literature values.<sup>31</sup>

### 7.3.7 2-((3-((4-Nitrophenyl)sulfonyl)phenyl)pyridine (3.26)



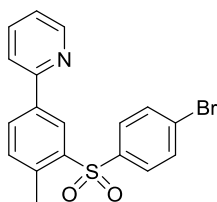
2-Phenylpyridine (2.0 mmol, 0.310 g) and 4-nitrophenylsulfonyl chloride (6.0 mmol, 1.326 g), were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give a yellow solid (28% yield). **mp** 158-161 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3647, 2980, 1605, 1586, 1531, 1460, 1350, 1301, 1150, 1102, 735, 679.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (dt,  $J = 4.8, 1.4$  Hz, 1H), 8.61 (t,  $J = 1.7$  Hz, 1H), 8.34 (d,  $J = 9.0$  Hz, 2H), 8.27 (ddd,  $J = 7.8, 1.7, 1.1$  Hz, 1H), 8.17 (d,  $J = 9.0$  Hz, 2H), 8.00 (ddd,  $J = 7.8, 1.9, 1.1$  Hz, 1H), 7.86 – 7.74 (m, 2H), 7.66 (t,  $J = 7.8$  Hz, 1H), 7.31 (ddd,  $J = 6.6, 4.8, 1.7$  Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.8, 150.4, 150.1, 147.3, 141.2, 140.7, 137.1, 132.3, 130.2, 129.1, 128.1, 126.4, 124.6, 123.3, 120.7. **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_4\text{S}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 363.0415, found: 363.0438.

### 7.3.8 2-(3-(Naphthalenesulfonyl)phenyl)pyridine (2.32) and (3.27)



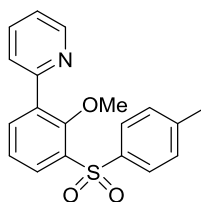
2-Phenylpyridine (2.0 mmol, 0.310 g) and naphthalen-2-ylsulfonyl chloride (6 mmol, 1.356 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (33% yield). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.68 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.64 (t, *J* = 1.7 Hz, 1H), 8.63 – 8.61 (m, 1H), 8.21 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.03 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.90 (d, *J* = 1.6 Hz, 2H), 7.87 – 7.81 (m, 1H), 7.81 – 7.71 (m, 2H), 7.64 – 7.53 (m, 3H), 7.29 – 7.23 (m, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 155.2, 149.9, 142.2, 140.7, 138.3, 137.2, 135.1, 132.2, 131.6, 129.9, 129.8, 129.5, 129.2, 129.2, 128.1, 128.0, 127.7, 126.1, 123.1, 122.7, 120.8. Data in accordance with literature values.<sup>31</sup>

### 7.3.9 2-(3-((4-Bromophenyl)sulfonyl)-4-methylphenyl)pyridine (3.28)



2-(*p*-Tolyl)pyridine (2.0 mmol, 0.338 g) and 4-bromophenylsulfonyl chloride (6.0 mmol, 1.518 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as a white solid (46% yield). **mp** 196-198 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2974, 1570, 1431, 1308, 1148, 1105, 1067, 1006, 808, 771, 742, 614.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.80 (d,  $J$  = 1.9 Hz, 1H), 8.70 (d,  $J$  = 4.7 Hz, 1H), 8.18 (dd,  $J$  = 7.9, 1.9 Hz, 1H), 7.84 – 7.73 (m, 2H), 7.74 (d,  $J$  = 8.7 Hz, 2H), 7.61 (d,  $J$  = 8.7 Hz, 2H), 7.34 (d,  $J$  = 8.0 Hz, 1H), 7.31 – 7.25 (m, 1H), 2.45 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3, 149.8, 140.3, 138.8, 138.5, 138.1, 137.2, 133.5, 132.4, 132.1, 129.3, 128.4, 127.8, 122.9, 120.6, 20.2. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{SBr}$   $[\text{M}+\text{H}]^+$ : 389.9941, found: 389.9960.

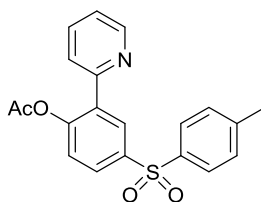
### 7.3.10 2-(2-Methoxy-3-tosylphenyl)pyridine (3.14)



2-(2-Methoxy)phenylpyridine (2.0 mmol, 0.37 g) and tosyl chloride (6 mmol, 1.134 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with dichloromethane/2-propanol (1:0.01) to give the title compound as a white solid (12% yield). **mp** 160-163 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2924, 1590, 1464, 1140, 1088, 989, 776, 685, 654.  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (d,  $J$  = 4.7 Hz, 1H), 8.17 (dd,  $J$  = 7.9, 1.8 Hz, 1H), 7.93 (dd,  $J$  = 7.7, 1.7 Hz, 1H), 7.86 (d,  $J$  = 8.3 Hz, 2H), 7.68 (d,  $J$  = 3.6 Hz, 2H), 7.35 (t,  $J$  = 7.8 Hz, 1H), 7.29 (d,  $J$  = 8.0 Hz, 2H), 7.24 (q,  $J$  = 4.7 Hz, 1H), 3.35 (s, 3H), 2.39 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.3, 154.5, 150.0, 144.0, 138.9, 137.5, 136.5, 135.6, 135.0, 130.0, 129.4, 128.2, 124.4, 124.2, 122.7, 62.2, 21.7. **HRMS** (ESI) calcd for  $\text{C}_{19}\text{H}_{18}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 340.1008, found: 340.1090.



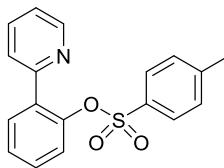
### 7.3.11 2-(2-Acetoxy-5-tosylphenyl)pyridine (3.17)



2-(2-Acetoxyphenyl)pyridine (2.0 mmol, 0.42 g) and tosyl chloride (6 mmol, 1.134 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (7% yield). **mp** 129-133 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2926, 1767, 1594, 1459, 1312, 1180, 1148, 1105, 1058, 810, 694, 649.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 – 8.50 (m, 1H), 8.24 (d,  $J$  = 2.2 Hz, 1H), 7.89 (dd,  $J$  = 8.5, 2.1 Hz, 1H), 7.76 (d,  $J$  = 8.0 Hz, 2H), 7.67 (t,  $J$  = 7.7 Hz, 1H), 7.46 (d,  $J$  = 7.8 Hz, 1H), 7.23 – 7.08 (m, 4H), 2.26 (s, 3H), 2.08 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.7, 153.9, 151.6, 149.5, 144.5, 139.9, 138.2, 136.7, 134.2, 130.5, 130.1, 128.9, 127.8, 124.7, 123.7, 123.1, 21.6, 21.0. **HRMS** (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{NO}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 368.0879, found: 368.1026.

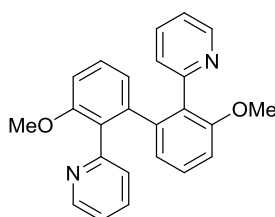
## 7.4 Other products obtained from *meta* sulfonation protocol

### 7.4.1 2-(2-Tosyloxyphenyl)pyridine (3.15)



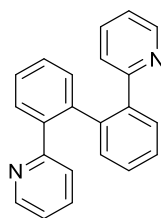
2-(2-Acetoxyphenyl)pyridine (2.0 mmol, 0.426 g) and tosyl chloride (6 mmol, 1.134 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with dichloromethane/2-propanol to give the title compound as a white crystalline solid (44% yield). **mp** 81-84 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3032, 2996, 1586, 1461, 1450, 1426, 1370, 1157, 1087, 1058, 855, 773, 659.  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (s, 1H), 7.69 – 7.56 (m, 3H), 7.45 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.24 (d,  $J$  = 8.3 Hz, 2H), 7.21 – 7.13 (m, 1H), 6.99 (d,  $J$  = 8.0 Hz, 2H), 2.34 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.2, 149.2, 146.6, 145.0, 135.9, 133.9, 131.6, 131.4, 129.9, 129.4, 128.1, 127.6, 125.2, 124.0, 122.0, 21.7. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 326.0851, found: 326.0866.

#### 7.4.2 2,2'-(3,3'-Dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dipyridine (3.16)



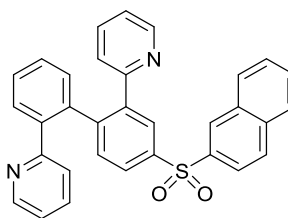
2-(2-Methoxyphenyl)pyridine (2.0 mmol, 0.370 g) and tosyl chloride (6 mmol, 1.134 g) were reacted together according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:1:0.01) to give the title compound as a white solid (37% yield). **mp** 118-120 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2923, 1734, 1594, 1376, 1255, 1141, 1088, 870, 782, 662, 681.  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ) 8.54 (d,  $J$  = 4.5 Hz, 1H), 7.62 – 7.36 (m, 1H), 7.26 (s, 1H), 7.12 – 7.07 (m, 1H), 7.04 (t,  $J$  = 8.0 Hz, 1H), 6.78 (d,  $J$  = 8.3 Hz, 1H), 6.57 (dd,  $J$  = 7.7, 0.8 Hz, 1H), 3.72 (s, 2H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8, 156.2, 148.2, 141.6, 135.7, 128.9, 128.1, 126.6, 123.6, 121.4, 109.4, 55.8. **HRMS** (ESI) calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 369.1603, found: 369.1744.

#### 7.4.3 2,2'-Di(pyridin-2-yl)-1,1'-biphenyl (2.31)



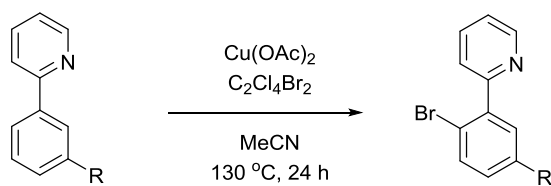
2-Phenylpyridine (2.0 mmol, 0.310 g) and 2-naphthalenesulfonyl chloride (6 mmol, 1.356 g) were reacted together according to the general procedure in PrCN before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:1:0.01) to give the title compound as a white solid (9% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d,  $J = 4.7$  Hz, 1H), 7.59 – 7.48 (m, 1H), 7.45 – 7.35 (m, 3H), 7.31 (td,  $J = 7.7, 1.6$  Hz, 1H), 7.00 (dd,  $J = 7.0, 5.4$  Hz, 1H), 6.76 (d,  $J = 7.9$  Hz, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0, 148.9, 139.8, 139.8, 135.3, 131.3, 130.0, 128.6, 127.8, 124.4, 121.2. Data in accordance with literature values.<sup>176</sup>

#### 7.4.4 2-(2-(2-Pyridylphenyl)-5-(naphthalen-2-ylsulfonyl)phenyl)pyridine (2.33)



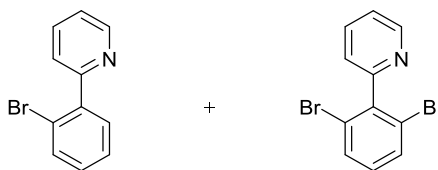
2-Phenylpyridine (2.0 mmol, 0.310 g) and 2-naphthalenesulfonyl chloride (6 mmol, 1.356 g) were reacted together according to the general procedure in PrCN, before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:1:0.01) to give the title compound as a brown oil (5% yield).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (d,  $J$  = 4.6 Hz, 1H), 8.58 (d,  $J$  = 4.6 Hz, 1H), 8.56 – 8.50 (m, 1H), 8.36 (d,  $J$  = 1.8 Hz, 1H), 8.18 – 8.04 (m, 2H), 8.04 – 7.77 (m, 5H), 7.76 – 7.53 (m, 5H), 7.52 – 7.36 (m, 2H), 7.17 (td,  $J$  = 7.6, 1.2 Hz, 1H), 7.11 – 7.02 (m, 1H), 6.72 (d,  $J$  = 8.2 Hz, 1H), 6.61 (d,  $J$  = 7.1 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  148.7, 138.4, 138.1, 138.0, 135.1, 132.4, 132.2, 131.1, 130.5, 129.7, 129.5, 129.5, 129.4, 129.3, 129.3, 129.2, 129.1, 129.0, 128.8, 127.9, 127.7, 127.6, 127.4, 124.6, 124.1, 122.8, 122.7, 122.7, 122.6, 118.2. **HRMS** (ESI) calcd for  $\text{C}_{32}\text{H}_{22}\text{N}_2\text{O}_2\text{SNa}$   $[\text{M}+\text{Na}]^+$ : 521.1299, found: 521.1337.

## 7.5 General procedure for the *ortho* bromination of 2-arylpyridines



$\text{Cu}(\text{OAc})_2$  (1.0 mmol, 0.182 g), 2-arylpyridine (1.0 mmol),  $\text{C}_2\text{Cl}_4\text{Br}_2$  (2.0 mmol, 0.651 g) and acetonitrile (5.0 mL) were added to a carousel tube and heated to  $130\text{ }^\circ\text{C}$  with stirring for 24 h. After cooling to room temperature the reaction mixture was washed with sat. aq.  $\text{NaHSO}_3$  (50 mL), extracted with dichloromethane (3 x 50 mL), filtered through celite, dried over  $\text{MgSO}_4$ , filtered again and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel.

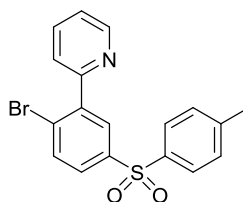
### 7.5.1 2-(2-Bromophenyl)pyridine (**3.12**)



2-Phenylpyridine (1.0 mmol, 0.143 mL) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a colourless oil (61% yield).  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.73 (ddd,  $J = 4.9, 1.7, 0.9$  Hz, 1H), 7.76 (td,  $J = 7.7, 1.8$  Hz, 1H), 7.69 (dd,  $J = 8.0, 1.0$  Hz, 1H), 7.61 (d,  $J = 7.9$  Hz, 1H), 7.55 (dd,  $J = 7.6, 1.8$  Hz, 1H), 7.41 (td,  $J = 7.5, 1.2$  Hz, 1H), 7.35 – 7.20 (m, 2H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 149.5, 141.3, 136.1, 133.5, 131.6, 129.9, 127.7, 125.0, 122.7, 121.9. Data in accordance with literature values.<sup>73</sup>

2-(2,6-dibromophenyl)pyridine (**3.13**) was also obtained as a byproduct, as a colourless oil (28% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.73 (ddd,  $J = 4.9, 1.7, 1.0$  Hz, 1H), 7.80 (td,  $J = 7.7, 1.8$  Hz, 1H), 7.61 (d,  $J = 8.1$  Hz, 2H), 7.37 – 7.24 (m, 2H), 7.10 (t,  $J = 8.1$  Hz, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 149.7, 141.9, 136.7, 132.1, 130.8, 124.8, 124.0, 123.3. Data in accordance with literature values.<sup>73</sup>

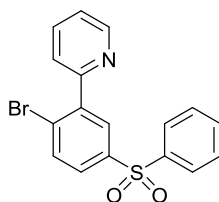
### 7.5.2 2-(2-Bromo-5-tosylphenyl)pyridine (3.29)



2-(3-Tosylphenyl)pyridine (1.0 mmol, 0.309 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (87% yield). **mp** 198-200 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2925, 1592, 1478, 1402, 1311, 1296, 1151, 1107, 814, 692, 646.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (d,  $J$  = 4.7 Hz, 1H), 8.50 (d,  $J$  = 2.3 Hz, 1H), 8.12 (d,  $J$  = 8.2 Hz, 1H), 8.02 (t,  $J$  = 8.5 Hz, 1H), 7.90 (d,  $J$  = 8.2 Hz, 2H), 7.84 (dd,  $J$  = 8.7, 2.1 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.40 – 7.31 (m, 2H), 7.15 (d,  $J$  = 8.7 Hz, 1H), 2.46 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.2, 155.9, 145.6, 143.8, 139.4, 138.7, 131.4, 130.8, 130.0, 127.4, 126.5, 122.7, 119.7, 118.6, 21.6. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{SBr}$   $[\text{M}+\text{H}]^+$ : 389.9986, found: 390.0062.

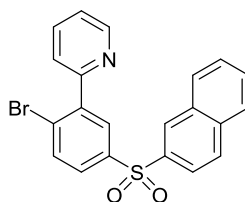


### 7.5.3 2-(2-Bromo-5-(phenylsulfonyl)phenyl)pyridine (3.36)



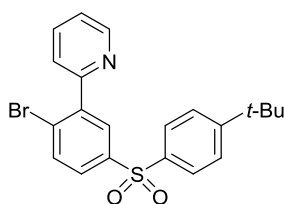
2-(3-(Phenylsulfonyl)phenyl)pyridine (1.0 mmol, 0.295 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (83% yield). **mp** 169-172 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2922.43, 1586.95, 1450.07, 1301.29, 1146.74, 1097.84, 770.57, 710.85, 681.18, 610.70.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (d,  $J$  = 4.3 Hz, 1H), 8.08 (s, 1H), 7.9 (d,  $J$  = 6.9 Hz, 2H), 7.77 (d,  $J$  = 1.2 Hz, 2H), 7.73 (dd,  $J$  = 7.7, 1.7 Hz, 1H), 7.56 – 7.38 (m, 4H), 7.29 (ddd,  $J$  = 7.7, 5.0, 1.0 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.7, 149.8, 142.6, 141.2, 141.1, 136.3, 134.5, 133.6, 130.4, 129.5, 128.4, 127.8, 124.6, 123.2. **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{12}\text{NO}_2\text{SBrNa}$   $[\text{M}+\text{Na}]^+$ : 395.9669, found: 395.9677.

#### 7.5.4 2-(2-Bromo-5-(naphthalen-2-ylsulfonyl)phenyl)pyridine (3.37)



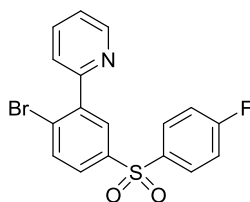
2-(3-(Naphthalen-2-ylsulfonyl)phenyl)pyridine (1.0 mmol, 0.345 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (79% yield). **mp** 185-188 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2983, 1587, 1462, 1432, 1303, 1152, 1102, 992, 801, 773, 655.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.69 (d,  $J$  = 4.3 Hz, 1H), 8.57 (s, 1H), 8.14 (d,  $J$  = 2.0 Hz, 1H), 7.97 – 7.75 (m, 7H), 7.64 – 7.53 (m, 3H), 7.33 (dd,  $J$  = 7.5, 0.8, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.4, 149.4, 142.1, 141.3, 137.8, 136.7, 135.2, 134.6, 132.3, 130.5, 129.9, 129.5, 129.4, 129.3, 128.7, 128.0, 127.8, 127.7, 124.8, 123.3, 122.6. **HRMS** (ESI) calcd for  $\text{C}_{21}\text{H}_{15}\text{NO}_2\text{SBr}$   $[\text{M}+\text{H}]^+$ : 424.0007, found: 424.0029.

#### 7.5.5 2-(2-Bromo-5-((4-(tert-butyl)phenyl)sulfonyl)phenyl)pyridine (3.38)



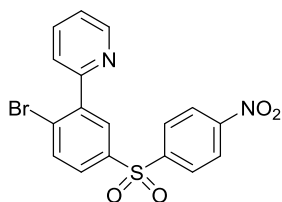
2-(3-((4-tert-Butylphenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.351 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a yellow solid (75% yield). **mp** 125-128 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3087, 2964, 1587, 1449, 1303, 1150, 1096, 1084, 825, 752, 703.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (ddd,  $J = 4.9, 1.7, 1.0$  Hz, 1H), 8.08 (t,  $J = 1.3$  Hz, 1H), 7.85 (d,  $J = 8.8$  Hz, 2H), 7.79 (d,  $J = 1.3$  Hz, 2H), 7.77 (dd,  $J = 7.7, 1.8$  Hz, 1H), 7.54 (dt,  $J = 7.9, 1.0$  Hz, 1H), 7.50 (d,  $J = 8.8$  Hz, 1H), 7.32 (ddd,  $J = 7.6, 4.9, 1.1$  Hz, 1H), 1.29 (s, 9H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.5, 156.7, 149.6, 142.4, 141.5, 138.0, 136.3, 134.4, 130.3, 128.4, 127.7, 127.6, 126.5, 124.6, 123.2, 36.2, 31.0. **HRMS** (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{NO}_2\text{SBrNa}$   $[\text{M}+\text{Na}]^+$ : 452.0295, found: 452.0303.

### 7.5.6 2-(2-Bromo-5-((4-fluorophenyl)sulfonyl)phenyl)pyridine (3.39)



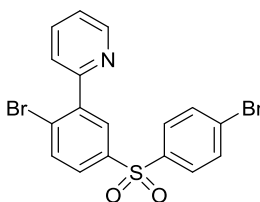
2-(3-((4-Fluorophenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.313 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (72% yield). **mp** 152-156 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3072, 2924, 1585, 1431, 1107, 844, 770, 660.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.62 (d,  $J$  = 4.4 Hz, 1H), 8.06 (s, 1H), 7.92 (dd,  $J$  = 8.7, 5.0 Hz, 2H), 7.72 (m, 3H), 7.50 (d,  $J$  = 7.8 Hz, 1H), 7.24 (ddd,  $J$  = 7.2, 4.7, 1.5, 1H), 7.09 (t,  $J$  = 8.5 Hz, 2H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  165.6 (d,  $J$  = 256.6 Hz), 156.5, 149.7, 142.6, 141.0, 137.07 (d,  $J$  = 3.2 Hz), 136.4, 134.6, 130.66 (d,  $J$  = 9.7 Hz), 130.4, 128.3, 128.0, 124.6, 123.3, 116.8 (d,  $J$  = 22.7 Hz). **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{12}\text{NO}_2\text{SFB}$   $[\text{M}+\text{H}]^+$ : 391.9756, found: 391.9783.

### 7.5.7 2-(2-Bromo-5-((4-nitrophenyl)sulfonyl)phenyl)pyridine (3.40)



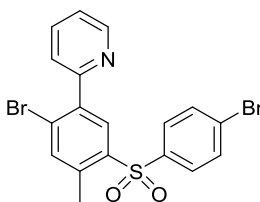
2-(3-((4-Nitrophenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.340 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (68% yield). **mp** 143-146 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  1587, 1448, 1334, 1345, 1102, 1014, 854, 827, 737, 630.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (d,  $J$  = 4.8 Hz, 1H), 8.30 (d,  $J$  = 8.9 Hz, 2H), 8.11 (d,  $J$  = 9.0 Hz, 2H), 8.08 (d,  $J$  = 2.2 Hz, 1H), 7.84 (d,  $J$  = 8.4 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.56 (d,  $J$  = 7.9 Hz, 1H), 7.33 (ddd,  $J$  = 7.6, 4.9, 1.1 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.2, 150.5, 149.7, 146.8, 142.9, 139.6, 136.3, 134.9, 130.8, 129.2, 129.0, 128.6, 124.7, 124.6, 123.4. **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_4\text{SBr}$   $[\text{M}+\text{H}]^+$ : 418.9701, found: 418.9719.

### 7.5.8 2-(2-Bromo-5-((4-bromophenyl)sulfonyl)phenyl)pyridine (3.41)



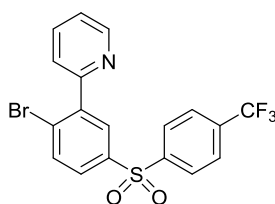
2-(3-((4-Bromophenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.372 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (71% yield). **mp** 126-130 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2923, 2853, 1734, 1592, 1577, 1388, 1325, 1151, 1102 1007, 816, 748, 707.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (d,  $J$  = 4.2 Hz, 1H), 8.06 (d,  $J$  = 1.8 Hz, 1H), 7.77 (td,  $J$  = 9.3, 8.4, 3.0 Hz, 5H), 7.60 (d,  $J$  = 8.7 Hz, 2H), 7.54 (d,  $J$  = 7.9 Hz, 1H), 7.31 (ddd,  $J$  = 7.6, 4.9, 1.1 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.4, 149.8, 142.6, 140.6, 140.0, 136.4, 134.7, 132.8, 130.4, 129.3, 128.9, 128.4, 128.1, 124.6, 123.3. **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{12}\text{NO}_2\text{SBr}_2$   $[\text{M}+\text{H}]^+$ : 451.8955, found: 451.8961.

### 7.5.9 2-(2-Bromo-5-((4-bromophenyl)sulfonyl)-4-methylphenyl)pyridine (3.42)



2-(3-((4-Bromophenyl)sulfonyl)-4-methylphenyl)pyridine (1.0 mmol, 0.387 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (76% yield). **mp** 162-166 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3088, 2927, 1712, 1571, 1456, 1304, 1148, 1058, 1007, 892, 825, 751, 733.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.74 (ddd,  $J = 4.9, 1.8, 0.9$  Hz, 1H), 8.36 (s, 1H), 7.87 – 7.71 (m, 3H), 7.69 – 7.54 (m, 4H), 7.35 (ddd,  $J = 7.6, 4.9, 1.2$  Hz, 1H), 2.43 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.5, 149.6, 139.9, 139.8, 139.1, 138.0, 137.4, 136.3, 132.5, 132.3, 129.3, 128.7, 128.0, 124.8, 123.1, 19.8. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{14}\text{NO}_2\text{SBr}_2$   $[\text{M}+\text{H}]^+$ : 467.9013, found: 467.9096.

#### 7.5.10 2-(2-Bromo-5-((4-(trifluoromethyl)phenyl)sulfonyl)phenyl)pyridine (3.43)

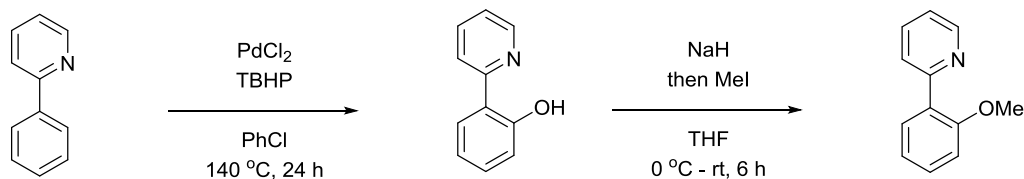


2-(3-((4-(Trifluoromethyl)phenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.363 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/NEt<sub>3</sub> (4:1:0.01) to give the title compound as a white solid (72% yield). **mp** 94-98 °C. **IR** (neat, cm<sup>-1</sup>)  $\nu$  1591, 1403, 1322, 1156, 1133, 1105, 1060, 1014, 826, 717. **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$  8.72 (ddd,  $J$  = 4.8, 1.7, 0.9 Hz, 1H), 8.14 – 8.04 (m, 3H), 7.90 – 7.71 (m, 5H), 7.58 (dt,  $J$  = 7.9, 0.9 Hz, 1H), 7.35 (ddd,  $J$  = 7.6, 4.9, 1.1 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  156.3, 149.7, 144.6, 142.8, 140.1, 136.3, 135.1 (q,  $J$  = 33.1 Hz), 134.7, 131.9, 130.6, 129.3, 128.5, 128.4 (d,  $J$  = 10.8 Hz), 126.6 (q,  $J$  = 3.7 Hz), 124.9, 124.6, 123.3, 121.2. **HRMS** (ESI) calcd for C<sub>18</sub>H<sub>12</sub>NO<sub>2</sub>SF<sub>3</sub>Br [M+H]<sup>+</sup>: 441.9724, found: 441.9737.



## 7.6 Other *ortho* Functionalisations

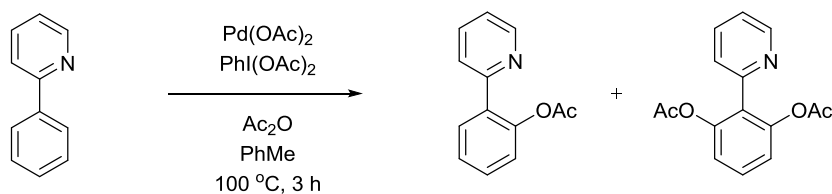
### 7.6.1 2-(2-Methoxyphenyl)pyridine (3.9)



$\text{PdCl}_2$  (0.05 mmol, 8.9 mg), 2-phenylpyridine (2.0 mmol, 0.286 mL), *t*-butylhydroperoxide (TBHP) (70% solution in water, 6.0 mmol, 1.0 mL) and chlorobenzene (5.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to  $140\text{ }^\circ\text{C}$  with stirring for 24 h. After cooling to room temperature the reaction mixture was filtered through celite, dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography eluting with dichloromethane to give the phenolic intermediate (3.8) as a yellow oil (52% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  13.76 (s, 1H), 8.47 (d,  $J = 4.8$  Hz, 1H), 7.88 (d,  $J = 8.3$  Hz, 1H), 7.78 (ddd,  $J = 8.4, 4.7, 2.0$  Hz, 2H), 7.32 (ddd,  $J = 8.5, 7.4, 1.6$  Hz, 1H), 7.20 (ddd,  $J = 7.2, 5.1, 0.9$  Hz, 1H), 7.06 (dd,  $J = 8.3, 1.2$  Hz, 1H), 6.96 – 6.85 (m, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  160.1, 157.9, 145.9, 138.0, 131.7, 126.3, 121.7, 119.3, 119.0, 118.9, 118.8. Data in accordance with literature values.<sup>73</sup>

The phenolic intermediate (1.0 mmol, 0.172 g) was added to anhydrous THF and cooled to  $0\text{ }^\circ\text{C}$  before NaH was added and stirred for 1 h at  $0\text{ }^\circ\text{C}$ . Methyl iodide (1.2 mmol, 0.062 mL) was then added, warmed to room temperature and stirred for 5 h. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 20 mL), dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The crude mixture was taken up in acetonitrile (50 mL) and washed with hexane (3 x 50 mL) before the solvent was removed *in vacuo* and purified by flash column chromatography eluting with dichloromethane to give the title compound as an orange oil (98% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (ddd,  $J = 4.9, 1.8, 0.9$  Hz, 1H), 7.87 – 7.74 (m, 2H), 7.68 (td,  $J = 7.7, 1.9$  Hz, 1H), 7.37 (ddd,  $J = 8.3, 7.4, 1.8$  Hz, 1H), 7.19 (ddd,  $J = 7.4, 4.9, 1.2$  Hz, 1H), 7.08 (td,  $J = 7.5, 1.1$  Hz, 1H), 6.99 (d,  $J = 9.0$  Hz, 1H), 3.84 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.1, 156.2, 149.5, 135.9, 131.3, 130.2, 129.2, 125.3, 121.9, 121.2, 111.5, 55.8. Data in accordance with literature values.<sup>177</sup>

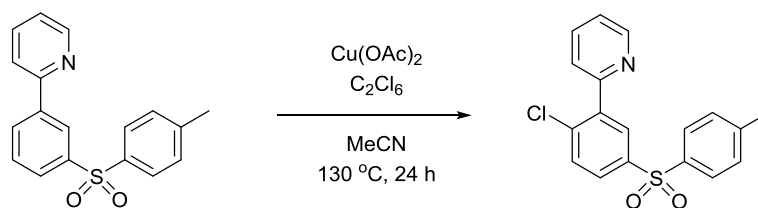
### 7.6.2 2-(2-Acetoxyphenyl)pyridine (3.10)



Pd(OAc)<sub>2</sub> (0.05 mmol, 11.2 mg), 2-phenylpyridine (1.0 mmol, 0.14 mL), PhI(OAc)<sub>2</sub> (1.5 mmol, 0.483 g), Ac<sub>2</sub>O (1.0 mL) and toluene (5.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to 100 °C with stirring for 3 h. After cooling to room temperature the reaction mixture was filtered through celite and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with hexanes/EtOAc (4:1) to give the title compound as a yellow oil (53% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.69 – 8.61 (m, 1H), 7.67 (td, *J* = 7.3, 1.8 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.38 (td, *J* = 7.6, 1.8 Hz, 1H), 7.30 (td, *J* = 7.5, 1.3 Hz, 1H), 7.18 (ddd, *J* = 7.6, 4.9, 1.0 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 2.13 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.4, 155.7, 149.5, 148.1, 136.4, 133.1, 130.8, 129.7, 126.4, 123.6, 123.3, 122.3, 21.0. Data in accordance with literature values.<sup>72</sup>

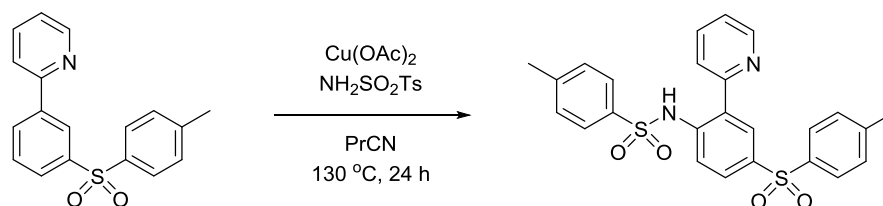
2-(2,6-diacetoxyphenyl)pyridine (3.11) was also obtained as an orange solid (15% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.66 – 8.60 (m, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.36 (t, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.20 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 1.94 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.1, 152.3, 149.5, 149.3, 136.3, 129.6, 127.5, 125.4, 122.8, 120.9, 20.8. Data in accordance with literature values.<sup>72</sup>

### 7.6.3 2-(2-Chloro-5-tosylphenyl)pyridine (3.30)



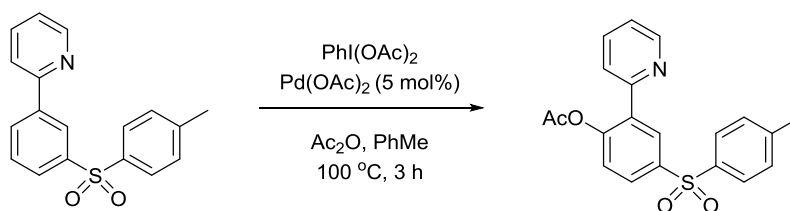
$\text{Cu}(\text{OAc})_2$  (1.0 mmol, 0.182 g), 2-(3-tosylphenyl)pyridine (1.0 mmol, 0.309 g),  $\text{C}_2\text{Cl}_6$  (2.0 mmol, 0.472 g) and acetonitrile (5.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to  $130\text{ }^\circ\text{C}$  with stirring for 24 h. After cooling to room temperature the crude reaction mixture was washed with sat. aq.  $\text{NaHSO}_3$  (50 mL), extracted with dichloromethane (3 x 50 mL), filtered through celite, dried over  $\text{MgSO}_4$ , filtered again and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with hexanes/ $\text{EtOAc}/\text{NEt}_3$  (1:1:0.01) to give the title compound as a white solid (67% yield). **mp**  $97\text{--}101\text{ }^\circ\text{C}$ . **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2152, 1590, 1287, 1148, 1085, 1030, 825, 791, 752, 713, 674.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (d,  $J = 4.3\text{ Hz}$ , 1H), 8.08 (d,  $J = 2.3\text{ Hz}$ , 1H), 7.85 – 7.63 (m, 4H), 7.51 (dd,  $J = 8.1, 2.8\text{ Hz}$ , 2H), 7.30 – 7.13 (m, 3H), 2.30 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.1, 149.8, 144.6, 141.0, 140.3, 138.1, 137.6, 136.3, 131.2, 130.7, 130.1, 128.4, 127.8, 124.8, 123.2, 21.7. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{SCl}$   $[\text{M}+\text{H}]^+$ : 344.0512, found: 344.0493.

#### 7.6.4 4-Methyl-*N*-(2-(pyridine-2-yl)-4-tosylphenyl)benzenesulfonamide (3.31)



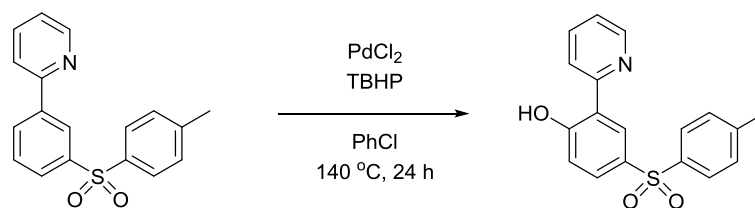
Cu(OAc)<sub>2</sub> (1.0 mmol, 0.182 g), 2-(3-tosylphenyl)pyridine (1.0 mmol, 0.309 g), *p*-toluenesulfonamide (2.0 mmol, 0.342 g) and PrCN (5.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to 130 °C with stirring for 24 h. After cooling to room temperature the reaction mixture was washed with sat. aq. NaHSO<sub>3</sub> (50 mL), extracted with dichloromethane (3 x 50 mL), filtered through celite, dried over MgSO<sub>4</sub>, filtered again and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with hexanes/EtOAc/NEt<sub>3</sub> (1:1:0.01) to give the title compound as a crystalline white solid (10% yield). **mp** 205-206 °C. **IR** (neat, cm<sup>-1</sup>) ν 2924, 1593, 1495, 1394, 1314, 1152, 1114, 1090, 932, 811, 690, 657. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) 13.19 (s, 1H), 8.66 (d, *J* = 3.6 Hz, 1H), 8.24 (s, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.74 (dt, *J* = 17.0, 8.5 Hz, 4H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.32 (m, 1H), 7.31 – 7.23 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.33 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 155.6, 147.3, 144.3, 143.9, 141.8, 138.6, 138.2, 136.5, 136.3, 130.0, 129.7, 129.3, 127.9, 127.6, 127.0, 124.9, 123.1, 122.4, 120.7, 21.6, 21.5. **HRMS** (ESI) calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup>: 479.1099, found: 479.1086.

### 7.6.5 2-(2-Acetoxy-5-tosylphenyl)pyridine (3.31)



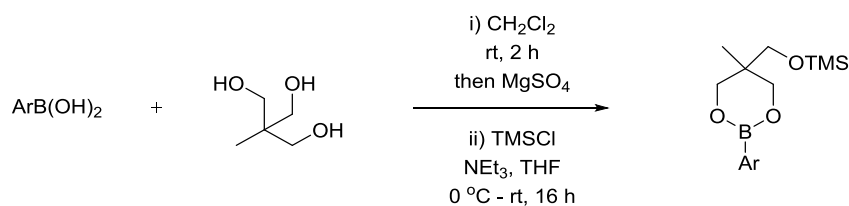
Pd(OAc)<sub>2</sub> (0.05 mmol, 11.2 mg), 2-(3-tosylphenyl)pyridine (1.0 mmol, 0.309 g), PhI(OAc)<sub>2</sub> (3.0 mmol, 0.966 g), Ac<sub>2</sub>O (3.0 mL) and toluene (3.0 mL) were added to carousel tube in air, sealed with a Teflon cap and heated to 100 °C with stirring for 3 h. After cooling to room temperature the reaction mixture was filtered through celite and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with hexanes/EtOAc/NEt<sub>3</sub> (4:1:0.01) to give the title compound as a white solid (82% yield). **mp** 129-133 °C. **IR** (neat, cm<sup>-1</sup>)  $\nu$  2926, 1767, 1594, 1459, 1312, 1180, 1148, 1105, 1058, 810, 694, 649. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.68 – 8.50 (m, 1H), 8.24 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.08 (m, 4H), 2.26 (s, 3H), 2.08 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.7, 153.9, 151.6, 149.5, 144.5, 139.9, 138.2, 136.7, 134.2, 130.5, 130.1, 128.9, 127.8, 124.7, 123.7, 123.1, 21.6, 21.0. **HRMS** (ESI) calcd for C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>S [M+H]<sup>+</sup>: 368.0879, found: 368.1026.

### 7.6.6 2-(2-Hydroxy-5-tosylphenyl)pyridine (3.32)



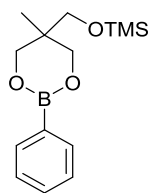
$\text{PdCl}_2$  (0.05 mmol, 8.9 mg), 2-(3-tosylphenyl)pyridine (1.0 mmol, 0.309 g), *t*-butylhydroperoxide (TBHP) (70% solution in water, 3.0 mmol, 0.52 mL) and chlorobenzene (5.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to  $140\text{ }^\circ\text{C}$  with stirring for 24 h. After cooling to room temperature the reaction mixture was filtered through celite and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with dichloromethane to give the title compound as an amorphous white solid (43% yield). **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3330, 3064, 2925, 1731, 1592, 1477, 1459, 1430, 1302, 1239, 1152, 1102, 821, 751, 635.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  15.26 (bs, 1H), 8.42 (d,  $J = 4.3$  Hz, 1H), 8.36 (d,  $J = 2.2$  Hz, 1H), 7.95 (d,  $J = 8.3$  Hz, 1H), 7.83 (td,  $J = 8.0, 1.7$  Hz, 1H), 7.75 (d,  $J = 8.3$  Hz, 2H), 7.71 (dd,  $J = 8.8, 2.2$  Hz, 1H), 7.27 (td,  $J = 9.0, 1.5$  Hz, 1H), 7.20 (d,  $J = 8.6$  Hz, 2H), 6.99 (d,  $J = 8.7$  Hz, 1H), 2.30 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.4, 156.1, 145.7, 143.8, 139.4, 138.4, 131.4, 130.6, 129.9, 127.3, 126.4, 122.7, 119.8, 119.5, 118.7, 21.6. **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 326.0850, found: 326.0865.

## 7.7 General procedure for the synthesis of silyl-protected dioxaborinanes



The required boronic acid (8.0 mmol) and anhydrous dichloromethane (32 mL) were added to a nitrogen-purged round-bottom flask and stirred for 5 min, before the addition of 2-(hydroxymethyl)-2-methylpropane-1,3-diol (8.0 mmol, 0.961 g). The reaction mixture was stirred at rt for 30 min until homogeneous. MgSO<sub>4</sub> was then added and stirred for another 30 min. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was taken up in anhydrous tetrahydrofuran (16 mL) under nitrogen and cooled to 0 °C, before the addition of NEt<sub>3</sub> (16 mmol, 2.2 mL) followed by TMSCl (12 mmol, 1.51 mL). The reaction mixture was warmed to rt and stirred for 16 h, before being quenched with water (50 mL), extracted with ethyl acetate (3 × 50 mL), dried over MgSO<sub>4</sub>, filtered and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel.<sup>178</sup>

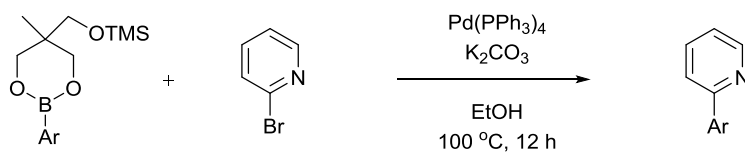
#### 7.7.1 Trimethyl((5-methyl-2-phenyl-1,3,2-dioxaborinan-5-yl)methoxy)silane (6.9)



Phenylboronic acid (8.0 mmol, 0.968 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc (9:1) to give the title compound as a white solid (93% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.81 (d, *J* = 6.7 Hz, 2H), 7.57 – 7.29 (m, 3H), 4.03 (d, *J* = 10.9 Hz, 2H), 3.78 (d, *J* = 10.9 Hz, 2H), 3.52 (s, 2H), 0.95 (s, 3H), 0.11 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 134.5, 131.3, 128.2, 68.7, 65.2, 37.5, 18.3, 0.0. Data in accordance with literature values.<sup>178</sup>

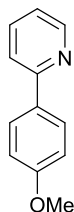


## 7.8 General procedure for the synthesis of 2-arylpyridines via Suzuki coupling



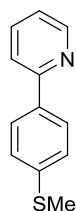
2-bromopyridine (2.0 mmol, 0.19 mL), dioxaborinane (3.0 mmol),  $\text{Pd(PPh}_3)_4$  (0.02 mmol, 23 mg),  $\text{K}_2\text{CO}_3$  (4.0 mmol, 0.55 g) and EtOH (5.0 mL) were added to a nitrogen-purged carousel tube, sealed with a Teflon cap and heated to  $100\text{ }^\circ\text{C}$  with stirring for 12 h. After cooling to room temperature the reaction mixture was washed with brine (50 mL), extracted with ethyl acetate (3 x 50 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel.

### 7.8.1 2-(4-Methoxyphenyl)pyridine (4.14)



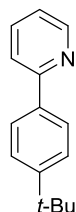
Trimethyl((5-methyl-2-(4-methoxyphenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.924 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (quantitative yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (d,  $J = 4.6\text{ Hz}$ , 1H), 7.95 (d,  $J = 8.9\text{ Hz}$ , 2H), 7.79 – 7.49 (m, 2H), 7.21 – 7.09 (m, 1H), 7.00 (d,  $J = 8.8\text{ Hz}$ , 2H), 3.86 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  160.5, 157.2, 149.6, 136.8, 132.1, 128.2, 121.5, 119.9, 114.2, 55.4. Data in accordance with literature values.<sup>179</sup>

### 7.8.2 2-(4-(Methylthio)phenyl)pyridine (4.15)



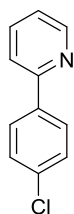
Trimethyl((5-methyl-2-(4-(methylthio)phenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.972 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (quantitative yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.68 (ddd, *J* = 4.9, 1.6, 1.1 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.81 – 7.67 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.23 (ddd, *J* = 6.7, 4.9, 1.6 Hz, 1H), 2.53 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.8, 149.5, 140.2, 137.2, 137.1, 127.3, 126.5, 122.1, 120.3, 15.6. Data in accordance with literature values.<sup>180</sup>

### 7.8.3 2-((4-*tert*-Butyl)phenyl)pyridine (4.16)



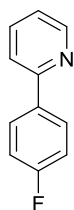
Trimethyl((5-methyl-2-(4-*tert*-butylphenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 1.002 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a colourless oil (quantitative yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.75 – 7.65 (m, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.27 – 7.13 (m, 1H), 1.38 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.4, 152.2, 149.6, 136.7, 126.6, 125.8, 121.9, 120.4, 34.7, 31.3. Data in accordance with literature values.<sup>181</sup>

### 7.8.4 2-(4-Chlorophenyl)pyridine (4.17)



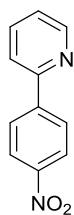
Trimethyl((5-methyl-2-(4-chlorophenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.936 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (73% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.74 (td, *J* = 7.7, 7.3, 1.3 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.16 (m, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.3, 149.8, 137.8, 136.9, 135.1, 129.0, 128.2, 122.4, 120.4. Data in accordance with literature values.<sup>178</sup>

#### 7.8.5 2-(4-Fluorophenyl)pyridine (4.18)



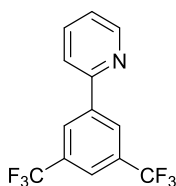
Trimethyl((5-methyl-2-(4-fluorophenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.888 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (quantitative yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.66 (d, *J* = 4.7 Hz, 1H), 8.05 – 7.89 (m, 2H), 7.71 (td, *J* = 7.6, 1.7 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.20 (ddd, *J* = 7.0, 4.8, 1.2 Hz, 1H), 7.14 (t, *J* = 8.7 Hz, 2H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 163.5 (d, *J* = 248.4 Hz), 156.4, 149.6, 136.9, 135.5 (d, *J* = 3.1 Hz), 128.7 (d, *J* = 8.3 Hz), 122.1, 120.3, 115.7 (d, *J* = 21.6 Hz). Data in accordance with literature values.<sup>182</sup>

#### 7.8.6 2-(4-Nitrophenyl)pyridine (4.19)



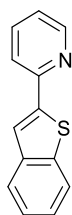
Trimethyl((5-methyl-2-(4-nitrophenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.969 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (64% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.76 (d, *J* = 4.7 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.91 – 7.78 (m, 2H), 7.36 (ddd, *J* = 6.6, 4.8, 1.8 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 154.8, 150.0, 137.5, 128.4, 127.8, 124.5, 124.1, 123.7, 121.5. Data in accordance with literature values.<sup>178</sup>

#### 7.8.7 2-(3,5-Ditrifluoromethylphenyl)pyridine (4.20)



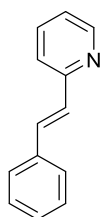
Trimethyl((5-methyl-2-(3,5-ditrifluoromethyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 1.243 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (79% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.75 (d, *J* = 5.0 Hz, 1H), 8.48 (s, 2H), 7.91 (s, 1H), 7.83 (qd, *J* = 7.4, 6.8, 1.4 Hz, 2H), 7.35 (ddd, *J* = 6.7, 4.8, 2.1 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 154.22, 150.27, 141.43, 137.40, 132.24 (q, *J* = 33.4 Hz), 127.08 (d, *J* = 27.7 Hz), 123.75, 123.5 (q, *J* = 135.8 Hz), 122.56 (p, *J* = 3.8 Hz), 120.76. Data in accordance with literature values.<sup>178</sup>

#### 7.8.8 2-(Benzothiophen-2-yl)pyridine (4.21)



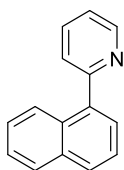
Trimethyl((5-methyl-2-(benzothiophen-2-yl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 1.002 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (91% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.63 (d,  $J = 4.1$  Hz, 1H), 7.94 – 7.84 (m, 1H), 7.83 – 7.73 (m, 3H), 7.68 (td,  $J = 7.7$ , 1.6 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.23 – 7.12 (m, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  152.5, 149.7, 144.8, 140.6, 140.5, 136.6, 125.0, 124.5, 124.1, 122.6, 122.6, 121.1, 119.6. Data in accordance with literature values.<sup>178</sup>

#### 7.8.9 2-Styrylpyridine (4.22)



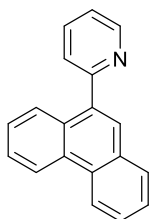
Trimethyl((5-methyl-2-styryl-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.912 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (quantitative yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (d,  $J = 4.0$  Hz, 1H), 7.52 (td,  $J = 7.9$ , 1.8 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.27 – 7.18 (m, 3H), 7.14 (1H, tt,  $J = 7.2$ , 1.7 Hz), 7.08 (d,  $J = 14.7$  Hz, 1H), 7.03 – 6.96 (m, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.6, 149.6, 136.8, 136.7, 133.0, 128.8, 128.5, 127.9, 127.2, 122.3, 122.2. Data in accordance with literature values.<sup>178</sup>

#### 7.8.10 2-(Naphthalen-1-yl)pyridine (4.24)



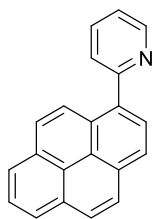
Trimethyl((5-methyl-2-(naphthalene-1-yl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 0.984 g), was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow oil (63% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.81 (d, *J* = 4.9 Hz, 1H), 8.14 – 8.04 (m, 1H), 7.92 (dd, *J* = 6.0, 2.0 Hz, 2H), 7.88 – 7.79 (m, 1H), 7.66 – 7.43 (m, 5H), 7.35 (dd, *J* = 7.5, 4.9 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 159.1, 149.3, 138.2, 136.7, 134.0, 131.1, 129.1, 128.4, 127.6, 126.6, 126.0, 125.6, 125.4, 125.2, 122.2. Data in accordance with literature values.<sup>183</sup>

#### 7.8.11 2-(Phenantren-9-yl)pyridine (4.25)



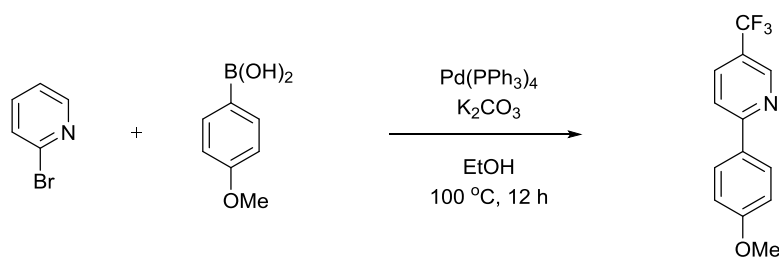
Trimethyl((5-methyl-2-(phenantren-9-yl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 1.134 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (37% yield). **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>) δ 8.84 (d, *J* = 4.4 Hz, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 7.3 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.88 (s, 1H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.75 – 7.54 (m, 5H), 7.35 (ddd, *J* = 7.5, 4.7, 0.8 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 159.4, 149.6, 137.3, 136.6, 131.5, 130.9, 130.6, 130.4, 129.1, 128.6, 127.2, 127.0, 126.9, 126.7, 126.7, 125.2, 123.1, 122.7, 122.2. Data in accordance with literature values.<sup>178</sup>

#### 7.8.12 2-(Pyren-1-yl)pyridine (4.26)



Trimethyl((5-methyl-2-(pyrene-1-yl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (3.0 mmol, 1.211 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a brown solid (23% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.90 (d, *J* = 4.9 Hz, 1H), 8.38 (d, *J* = 9.3 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 8.25 – 8.15 (m, 3H), 8.14 – 7.98 (m, 4H), 7.92 (td, *J* = 7.7, 1.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.42 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 159.3, 149.5, 136.9, 135.2, 131.6, 131.5, 130.9, 128.7, 128.2, 128.1, 127.7, 127.5, 126.2, 126.0, 125.5, 125.2, 125.1, 124.9, 124.9, 124.7, 122.1. Data in accordance with literature values.<sup>178</sup>

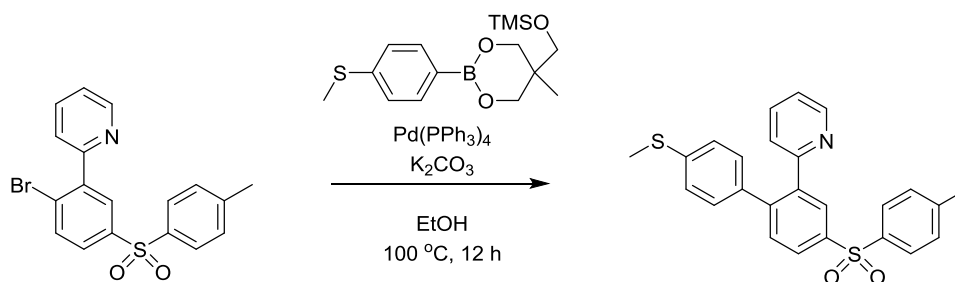
### 7.8.13 Synthesis of 2-(4-methoxyphenyl)-5-trifluoromethylpyridine (4.23)



4-Methoxyphenylboronic acid (3.0 mmol, 0.45 g), 2-chloro-5-trifluoromethylpyridine (2.0 mmol, 0.36 g),  $\text{Pd(PPh}_3)_4$  (0.02 mmol, 23 mg),  $\text{K}_2\text{CO}_3$  (4.0 mmol, 0.55 g) and EtOH (5.0 mL) were added to a nitrogen-purged carousel tube, sealed with a Teflon cap and heated to  $100\text{ }^\circ\text{C}$  with stirring for 12 h. After cooling to room temperature the reaction mixture was washed with brine (50 mL), extracted with ethyl acetate (3 x 50 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (87% yield).  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.90 (s, 1H), 8.01 (d,  $J = 8.9\text{ Hz}$ , 2H), 7.93 (dd,  $J = 8.4, 2.3\text{ Hz}$ , 1H), 7.78 (d,  $J = 8.4\text{ Hz}$ , 1H), 7.02 (d,  $J = 8.9\text{ Hz}$ , 2H), 3.88 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  161.4, 160.3 (d,  $J = 1.3\text{ Hz}$ ), 146.5 (q,  $J = 4.1\text{ Hz}$ ), 134.0 (q,  $J = 3.5\text{ Hz}$ ), 130.5, 128.8, 124.1 (q,  $J = 32.9\text{ Hz}$ ), 123.9 (q,  $J = 271.9\text{ Hz}$ ), 119.2, 114.4, 55.5. Data in accordance with literature values.<sup>184</sup>

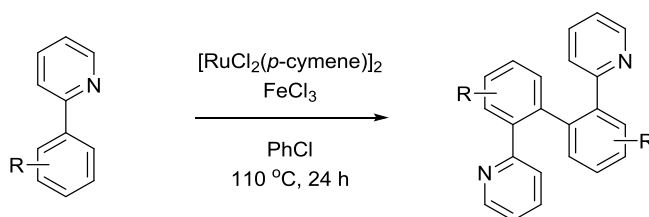


## 7.9 Synthesis of 2-(2-(4-methylthio)phenyl)-5-tosylphenylpyridine (3.45)



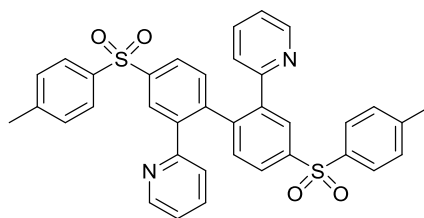
$\text{Pd(PPh}_3)_4$  (0.01 mmol, 0.012 g), 2-(2-bromo-5-tosylphenyl)pyridine (0.50 mmol, 0.195 g), trimethyl((5-methyl-2-(4-(methylthio)phenyl)-1,3,2-dioxaborinan-5-yl)methoxy)silane (0.75 mmol, 243 g),  $\text{K}_2\text{CO}_3$  (1.0 mmol, 0.138 g) and EtOH (3.0 mL) were added to a nitrogen-purged carousel tube, sealed with a Teflon cap and heated to 100 °C with stirring for 12 h. After cooling to room temperature the reaction mixture was then washed with sat. aq.  $\text{NaHCO}_3$ , extracted with dichloromethane, dried over  $\text{MgSO}_4$  and the solvent removed. The crude reaction mixture was then purified by flash column chromatography eluting with hexane/EtOAc/ $\text{NEt}_3$  (2:1:0.01) to give the title compound as a white solid (84% yield). **mp** 175-178 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  1592, 1458, 1315, 1280, 1153, 1094, 838, 816, 709, 662.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (d,  $J$  = 5.5 Hz, 1H), 8.21 (d,  $J$  = 1.9 Hz, 1H), 7.96 (dd,  $J$  = 8.1, 2.0 Hz, 1H), 7.87 (d,  $J$  = 8.3 Hz, 2H), 7.50 (d,  $J$  = 8.1 Hz, 1H), 7.44 (dd,  $J$  = 7.7, 1.7 Hz, 1H), 7.28 (d,  $J$  = 8.0 Hz, 2H), 7.14 (ddd,  $J$  = 7.5, 4.9, 1.0 Hz, 1H), 7.07 (d,  $J$  = 8.5 Hz, 2H), 7.00 (d,  $J$  = 8.6 Hz, 2H), 6.91 (d,  $J$  = 7.9 Hz, 1H), 2.42 (s, 3H), 2.37 (s, 3H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.4, 149.6, 144.7, 144.3, 141.0, 140.4, 138.6, 138.5, 136.0, 135.9, 131.4, 130.0, 129.9, 129.8, 127.9, 127.4, 125.9, 125.3, 122.2, 21.7, 15.5. **HRMS** (ESI) calcd for  $\text{C}_{25}\text{H}_{21}\text{NO}_2\text{S}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 454.0911, found: 454.0906

### 7.10 General Procedure for the Homocoupling 2-Arylpyridine Derivatives



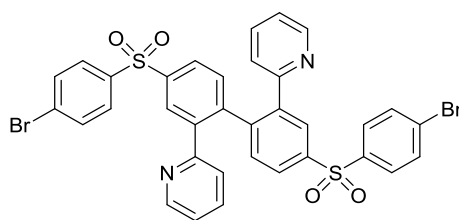
2-Arylpyridine (1.0 mmol),  $\text{FeCl}_3$  (0.8 mmol, 0.129 g),  $[\text{RuCl}_2(p\text{-cymene})]_2$  (0.025 mmol, 15.3 mg) and chlorobenzene (3.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to  $110\text{ }^\circ\text{C}$  with stirring for 24 h. After cooling to room temperature the reaction mixture was diluted with dichloromethane, filtered through Celite and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography on silica gel.

### 7.10.1 2,2'-(4,4'-Ditosyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine (3.33)



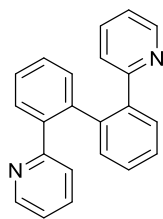
2-(3-Tosylphenyl)pyridine (1.0 mmol, 0.309 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (81% yield). **mp** 107-110 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2919, 1589, 1317, 1151, 1105, 809, 749, 708, 672, 660.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (d,  $J$  = 4.1 Hz, 2H), 8.00 (d,  $J$  = 1.6 Hz, 2H), 7.81 – 7.72 (m, 6H), 7.35 (td,  $J$  = 7.5, 1.8, 2H), 7.22 (dd,  $J$  = 8.4, 3.7 Hz, 6H), 7.03 (dd,  $J$  = 7.2, 2.1, 2H), 6.84 (d,  $J$  = 7.8 Hz, 2H), 2.33 (s, 6H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.2, 149.6, 144.4, 143.8, 141.6, 140.9, 138.4, 136.1, 132.1, 130.0, 129.2, 127.1, 127.8, 124.1, 122.3, 21.6. **HRMS** (ESI) calcd for  $\text{C}_{36}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_2$   $[\text{M}+\text{H}]^+$ : 617.1569, found: 617.1603.

### 7.10.2 2,2'-(4,4'-Di-(4-bromophenyl)sulfonyl)-[1,1'-biphenyl]-2,2'-diyl)dipyridine (3.34)



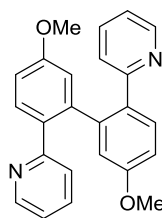
2-(3-(4-Bromophenyl)sulfonyl)pyridine (1.0 mmol, 0.374 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:1:0.01) to give the title compound as a white solid (63% yield). **mp** 126-130 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  1571, 1469, 1389, 1321, 1153, 1106, 1066, 1008, 813, 740, 629.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (d,  $J$  = 3.7 Hz, 1H), 8.01 (s, 1H), 7.78 – 7.73 (m, 3H), 7.58 (d,  $J$  = 7.8 Hz, 2H), 7.37 (t,  $J$  = 7.6 Hz, 1H), 7.28 – 7.17 (m, 1H), 7.10 – 6.99 (m, 1H), 6.88 (d,  $J$  = 7.8 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 149.4, 144.1, 141.0, 140.8, 140.4, 136.3, 132.7, 132.2, 129.3, 128.7, 127.2, 124.2, 122.5. **HRMS** (ESI) calcd for  $\text{C}_{34}\text{H}_{23}\text{N}_2\text{O}_4\text{S}_2\text{Br}_2$   $[\text{M}+\text{H}]^+$ : 746.9471, found: 746.9445.

### 7.10.3 2,2'-Di(pyridin-2-yl)-1,1'-biphenyl (4.2)



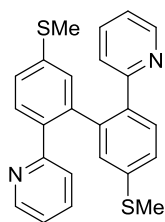
2-Phenylpyridine (0.155 g, 1.0 mmol) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (80% yield).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d,  $J$  = 4.7 Hz, 1H), 7.59 – 7.48 (m, 1H), 7.45 – 7.35 (m, 3H), 7.31 (td,  $J$  = 7.7, 1.6 Hz, 1H), 7.00 (dd,  $J$  = 7.0, 5.4 Hz, 1H), 6.76 (d,  $J$  = 7.9 Hz, 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0, 148.9, 139.8, 139.8, 135.3, 131.3, 130.0, 128.6, 127.8, 124.4, 121.2. Data in accordance with literature values.<sup>74</sup>

#### 7.10.4 2,2'-(5,5'-Dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dipyridine (4.27)



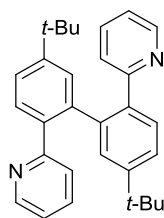
2-(4-Methoxyphenyl)pyridine (1.0 mmol, 0.185 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:4:0.01) to give the title compound as a green solid (60% yield). **mp** 114–116 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3001, 2935, 2834, 1710, 1600, 1587, 1567, 1460, 1426, 1295, 1274, 1223, 1027, 1017, 857.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (ddd,  $J = 4.9, 1.8, 0.9$  Hz, 2H), 7.49 (d,  $J = 9.0$  Hz, 2H), 7.29 (td,  $J = 7.8, 1.9$  Hz, 2H), 7.00 – 6.90 (m, 6H), 6.72 (dt,  $J = 8.0, 1.0$  Hz, 2H), 3.81 (s, 6H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7, 157.6, 148.8, 141.0, 135.1, 132.7, 131.5, 124.2, 120.8, 116.1, 113.6, 55.4. **HRMS** (ESI) calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 369.1603, found: 369.1607.

#### 7.10.5 2,2'-(5,5'-Bis(methylthio)-[1,1'-biphenyl]-2,2'-diyl)dipyridine (4.28)



2-(4-Methylthiophenyl)pyridine (1.0 mmol, 0.201 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a yellow solid (8% yield). **mp** 168-171 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3006, 2912, 1737, 1612, 1586, 1564, 1492, 1384, 1319, 1295, 1148, 1103, 1063, 1019, 990, 971, 952, 890, 861.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (d,  $J$  = 4.1 Hz, 2H), 7.53 (d,  $J$  = 8.2 Hz, 2H), 7.41 (td,  $J$  = 7.8, 1.7 Hz, 2H), 7.33 (dd,  $J$  = 8.3, 2.1 Hz, 2H), 7.27 (d,  $J$  = 1.9 Hz, 2H), 7.07 (ddd,  $J$  = 7.5, 4.9, 1.0 Hz, 2H), 6.84 (d,  $J$  = 7.9 Hz, 2H), 2.51 (s, 6H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.2, 148.7, 139.8, 139.5, 136.3, 135.6, 130.5, 128.2, 125.5, 124.4, 121.3, 15.4. **HRMS** (ESI) calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{S}_2$   $[\text{M}+\text{H}]^+$ : 401.1146, found: 401.1173.

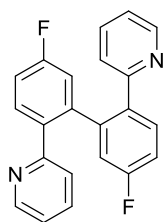
#### 7.10.6 2,2'-(5,5'-Di-*tert*-butyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine (4.29)



2-(4-*tert*-Butylphenyl)pyridine (1.0 mmol, 0.211 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (1:4:0.01) to give the title compound as a green solid (84% yield). **mp** 76-77 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3046, 2960, 2903, 2866, 1603, 1586, 1461, 1427, 1382, 1361, 1258, 1230, 1150, 1019, 893, 833.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (ddd,  $J = 4.9, 1.8, 0.9$  Hz, 2H), 7.56 (d,  $J = 8.1$  Hz, 2H), 7.41 – 7.29 (m, 4H), 7.08 (d,  $J = 2.1$  Hz, 2H), 7.04 – 6.91 (m, 4H), 1.15 (s, 18H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 151.0, 149.1, 139.6, 137.2, 135.2, 129.8, 129.2, 124.7, 124.3, 121.0, 34.4, 31.1. **HRMS** (ESI) calcd for  $\text{C}_{30}\text{H}_{32}\text{N}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 443.2463, found: 443.2494.

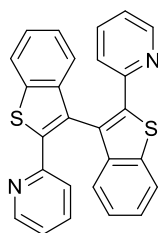


#### 7.10.7 2,2'-(5,5'-Difluoro-[1,1'-biphenyl]-2,2'-diyl)dipyridine (4.30)



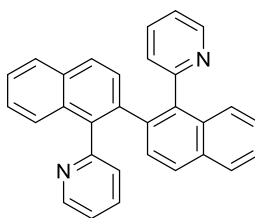
2-(4-Fluorophenyl)pyridine (1.0 mmol, 0.173 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a yellow solid (21% yield). **mp** 107–108 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3047, 3004, 1586, 1494, 1461, 1432, 1398, 1261, 1153, 1085, 1009, 988, 846, 830.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (d,  $J = 4.2$  Hz, 2H), 7.48 (dd,  $J = 8.3, 6.0$  Hz, 2H), 7.33 (td,  $J = 7.8, 1.7$  Hz, 2H), 7.12 – 7.02 (m, 4H), 7.00 (ddd,  $J = 7.6, 4.8, 0.8$  Hz, 2H), 6.75 (d,  $J = 7.9$  Hz, 2H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (d,  $J = 248.9$  Hz), 156.7, 148.9, 140.8 (dd,  $J = 7.9, 1.4$  Hz), 135.9 (d,  $J = 3.2$  Hz), 135.5, 132.1 (d,  $J = 8.5$  Hz), 124.1, 121.4, 117.6 (d,  $J = 22.0$  Hz), 115.0 (d,  $J = 21.0$  Hz). **HRMS** (ESI) calcd for  $\text{C}_{22}\text{H}_{15}\text{F}_2\text{N}_2$   $[\text{M}+\text{H}]^+$ : 345.1203, found: 345.1218.

#### 7.10.8 2,2'-Di(pyridin-2-yl)-3,3'-bibenzo[*b*]thiophene (4.31)



2-(Benzothiophen-2-yl)pyridine (1.0 mmol, 0.211 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (9:1:0.01) to give the title compound as a yellow solid (19% yield). **mp** 210-212 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3045, 3000, 2922, 2852, 1585, 1558, 1529, 1462, 1428, 1336, 1289, 1246, 1190, 1151, 1092, 1071, 990, 957, 941, 838.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (dd,  $J = 4.4, 1.5$  Hz, 1H), 7.90 (d,  $J = 8.0$  Hz, 1H), 7.31 (ddd,  $J = 8.1, 6.6, 1.7$  Hz, 1H), 7.24 – 7.06 (m, 3H), 7.01 – 6.87 (m, 2H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  151.9, 149.4, 143.0, 140.5, 139.9, 136.8, 127.7, 125.9, 124.8, 123.7, 122.7, 122.6, 120.9. **HRMS** (ESI) calcd for  $\text{C}_{26}\text{H}_{17}\text{N}_2\text{S}_2$   $[\text{M}+\text{H}]^+$ : 421.0833, found: 421.0867.

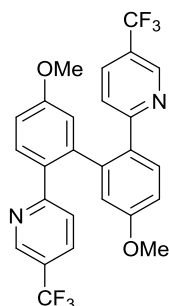
#### 7.10.9 1,1'-Di(pyridin-2-yl)-2,2'-binaphthalene (4.32)



2-(Naphthalen-1-yl)pyridine (1.0 mmol, 0.205 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a purple solid (49% yield). **mp** 262-263 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3052, 1583, 1560, 1502, 1471, 1426, 1373, 1232, 1145, 1088, 1047, 992, 870, 834, 819.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (br s, 2H), 7.79 (d,  $J$  = 7.6 Hz, 2H), 7.67 – 7.48 (m, 7H), 7.48 – 7.32 (m, 5H), 7.20 (d,  $J$  = 8.4 Hz, 2H), 7.13 (dd,  $J$  = 8.2, 4.9 Hz, 2H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.2, 149.0, 138.2, 137.0, 135.9, 132.5, 132.1, 129.2, 127.9, 127.2, 126.9, 126.4, 126.0, 125.7, 121.7. **HRMS** (ESI) calcd for  $\text{C}_{30}\text{H}_{20}\text{N}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 431.1524, found: 431.1576.

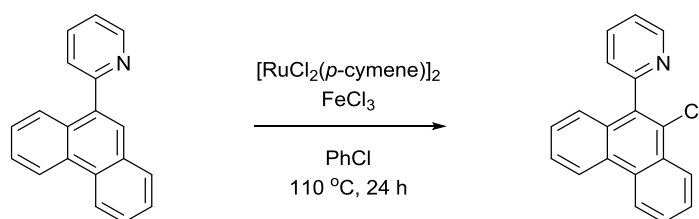
#### 7.10.10 2,2'-(5,5'-Bis(methoxy)-[1,1'-biphenyl]-2,2'-diyl)-5,5'-bis(trifluoromethyl)

##### dipyridine (4.33)



2-(4-Methoxyphenyl)-5-trifluoromethylpyridine (1.0 mmol, 0.253 g) was reacted according to the general procedure before purification by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a white solid (72% yield). **mp** 154-157 °C. **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  3042, 2973, 2842, 1603, 1571, 1474, 1389, 1329, 1298, 1232, 1198, 1164, 1126, 1084, 1025, 1013, 942, 878, 866, 820, 716.  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (s, 2H), 7.53 (d,  $J$  = 8.5 Hz, 4H), 7.00 (dd,  $J$  = 8.6, 2.7 Hz, 2H), 6.94 (d,  $J$  = 2.6 Hz, 2H), 6.87 (d,  $J$  = 8.3 Hz, 2H), 3.85 (s, 6H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  161.1 (d,  $J$  = 1.3 Hz), 160.5, 145.9 (q,  $J$  = 4.0 Hz), 141.1, 132.4 (q,  $J$  = 3.4 Hz), 132.0, 131.2, 123.8 (q,  $J$  = 540.1 Hz), 123.6 (q,  $J$  = 65.3 Hz), 123.5, 116.7, 113.8, 55.6. **HRMS** (ESI) calcd for  $\text{C}_{26}\text{H}_{18}\text{N}_2\text{O}_2\text{F}_6$   $[\text{M}+\text{H}]^+$ : 527.1170, found: 527.1248.

#### 7.10.11 2-(10-Chlorophenanthren-9-yl)pyridine (4.34)

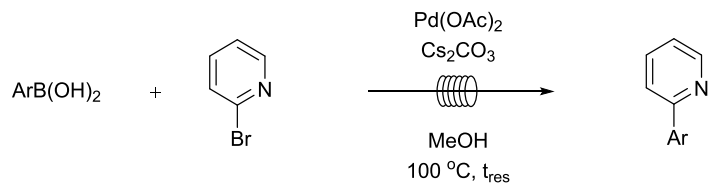


2-(Phenanthren-9-yl)pyridine (1.0 mmol, 0.255 g),  $\text{FeCl}_3$  (0.8 mmol, 0.129 g),  $[\text{RuCl}_2(p\text{-cymene})]_2$  (0.025 mmol, 15.3 mg) and chlorobenzene (3.0 mL) were added to a carousel tube in air, sealed with a Teflon cap and heated to  $110\text{ }^\circ\text{C}$  with stirring for 16 h. After cooling to room temperature the reaction mixture was diluted with dichloromethane, filtered through Celite and the solvent removed *in vacuo*. The crude reaction mixture was then purified by flash column chromatography eluting with hexanes/EtOAc/ $\text{NEt}_3$  (4:1:0.01) to give the title compound as a grey solid (21% yield). **mp**  $120\text{--}125\text{ }^\circ\text{C}$ . **IR** (neat,  $\text{cm}^{-1}$ )  $\nu$  2923, 2852, 1578, 1468, 1447, 1421, 1260, 1182, 1045, 893, 799, 773, 755, 745, 721, 626, 618, 604.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.87 (d,  $J = 4.4\text{ Hz}$ , 1H), 8.83 – 8.66 (m, 2H), 8.59 – 8.43 (m, 1H), 7.91 (td,  $J = 7.7, 1.6\text{ Hz}$ , 1H), 7.82 – 7.69 (m, 2H), 7.69 – 7.59 (m, 1H), 7.56 – 7.39 (m, 3H), 7.31 (d,  $J = 8.2\text{ Hz}$ , 1H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.4, 149.8, 136.8, 135.3, 131.7, 131.3, 130.0, 129.5, 129.3, 127.8, 127.6, 127.3, 126.9, 126.8, 126.1, 126.0, 122.8. **HRMS** (ESI) calcd for  $\text{C}_{19}\text{H}_{12}\text{NClNa}$   $[\text{M}+\text{Na}]^+$ : 312.0555, found: 312.0535.

### 7.11 Preparation of a Pd-dimer Complex (4.37)

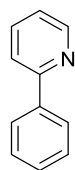
$\text{PdCl}_2(\text{MeCN})_2$  (0.1 mmol, 26 mg) and methanol (20 mL) were added to a round bottom flask under nitrogen and stirred at rt for 10 min. 2,2'-di(pyridin-2-yl)-1,1'-biphenyl (0.1 mmol, 31 mg) was then added and the reaction mixture stirred at reflux for 24 h. After cooling to room temperature the reaction mixture was filtered and the precipitate washed with methanol and dried in an oven overnight.

### 7.12 General Procedure for Suzuki Coupling in Flow



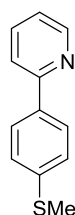
The catalyst solution was made up by addition of Pd(OAc)<sub>2</sub> (0.02 mmol, 4.5 mg) to MeOH (200 mL), which was stirred until uniform, filtered to remove any remaining particulates and decanted into 50 mL portions. A separate reagent solution was made up by addition of 2-bromopyridine (1.0 mmol, 0.158 g), boronic acid (1.05 mmol) and cesium carbonate (2.0 mmol, 0.650 g) to MeOH (50 mL), which was again stirred until uniform and filtered to remove particulates. The two solutions were assigned to opposing pumps and then pumped around the Vapourtec R-2+ module in conjunction with the R-4 reactor heater with a total residence time of 12 min. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a packed bed of glass beads to a length of 7 cm (volume 2 mL) and a stainless steel coil with a volume of 10 mL, giving a total reaction volume of 12 mL. The reaction column and coil was purged with MeOH (15 mL) and heated to 100 °C prior to introduction of the catalyst and reagent solutions. The temperature was maintained at 100 °C throughout and an additional portion of MeOH (15 mL) was pumped through the reactors after all of the catalyst and reagent solutions had been used. The post-reaction mixture was washed with brine (20 mL), extracted with ethyl acetate (3 × 10mL), dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel.

### 7.12.1 2-Phenylpyridine (6.2)



Phenylboronic acid (1.05 mmol, 0.122 g) was reacted according to the general procedure, before purification by flash column chromatography eluting with dichloromethane to give the title compound as a colourless oil (93 % yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.70 (d, *J* = 5.3 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 3.7 Hz, 2H), 7.54 – 7.37 (m, 3H), 7.27 – 7.13 (m, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.3, 149.6, 139.3, 136.8, 128.9, 128.7, 126.9, 122.1, 120.6. Data in accordance with literature values.<sup>185</sup>

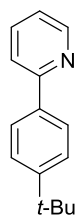
### 7.12.2 2-(4-(Methylthio)phenyl)pyridine (6.12)



4-(Methylthio)phenylboronic acid (1.05 mmol, 0.176 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (94% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.68 (ddd, *J* = 4.9, 1.6, 1.1 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.81 – 7.67 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.23 (ddd, *J* = 6.7, 4.9, 1.6 Hz, 1H), 2.53 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.8, 149.5, 140.2, 137.2, 137.1, 127.3, 126.5, 122.1, 120.3, 15.6. Data in accordance with literature values.<sup>180</sup>

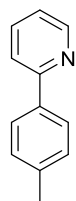


### 7.12.3 2-((4-*tert*-Butyl)phenyl)pyridine (6.13)



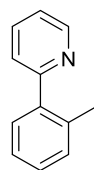
4-*tert*-Butylphenylboronic acid (1.05 mmol, 0.187 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a colourless oil (96% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.75 – 7.65 (m, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.27 – 7.13 (m, 1H), 1.38 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.4, 152.2, 149.6, 136.7, 126.6, 125.8, 121.9, 120.4, 34.7, 31.3. Data in accordance with literature values.<sup>181</sup>

### 7.12.4 2-(4-Tolyl)pyridine (6.14)



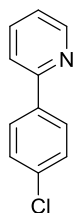
4-Methylphenylboronic acid (1.05 mmol, 0.142 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a colourless oil (91 % yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 5.0 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.61 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.17 (h, *J* = 4.4 Hz, 1H), 2.40 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 157.3, 149.5, 138.9, 136.7, 136.5, 129.4, 126.7, 121.7, 120.2, 21.2. Data in accordance with literature values.<sup>186</sup>

#### 7.12.5 2-(2-Tolyl)pyridine (6.15)



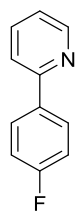
2-Methylphenylboronic acid (1.05 mmol, 0.142 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a colourless oil (90% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.69 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.74 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.33 – 7.21 (m, 4H), 2.37 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 160.0, 149.2, 140.4, 136.2, 135.8, 130.8, 129.7, 128.3, 125.9, 124.2, 121.7, 20.3. Data in accordance with literature values.<sup>187</sup>

#### 7.12.6 2-(4-Chlorophenyl)pyridine (6.16)



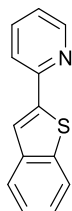
4-Chlorophenylboronic acid (1.05 mmol, 0.164 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (91% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.74 (td, *J* = 7.7, 7.3, 1.3 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.16 (m, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.3, 149.8, 137.8, 136.9, 135.1, 129.0, 128.2, 122.4, 120.4. Data in accordance with literature values.<sup>178</sup>

#### 7.12.7 2-(4-Fluorophenyl)pyridine (6.17)



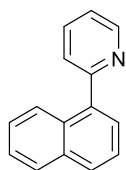
4-Fluorophenylboronic acid (1.05 mmol, 0.147 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow solid (88% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.66 (d, *J* = 4.7 Hz, 1H), 8.05 – 7.89 (m, 2H), 7.71 (td, *J* = 7.6, 1.7 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.20 (ddd, *J* = 7.0, 4.8, 1.2 Hz, 1H), 7.14 (t, *J* = 8.7 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.5 (d, *J* = 248.4 Hz), 156.4, 149.6, 136.9, 135.5 (d, *J* = 3.1 Hz), 128.7 (d, *J* = 8.3 Hz), 122.1, 120.3, 115.7 (d, *J* = 21.6 Hz). Data in accordance with literature values.<sup>182</sup>

#### 7.12.8 2-(Benzothiophen-2-yl)pyridine (6.18)



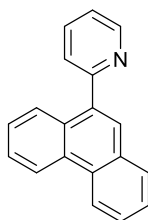
Benzothiophen-2-ylboronic acid (1.05 mmol, 0.187 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (95% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.63 (d, *J* = 4.1 Hz, 1H), 7.94 – 7.84 (m, 1H), 7.83 – 7.73 (m, 3H), 7.68 (td, *J* = 7.7, 1.6 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.23 – 7.12 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 52.5, 149.7, 144.8, 140.6, 140.5, 136.6, 125.0, 124.5, 124.1, 122.6, 122.6, 121.1, 119.6. Data in accordance with literature values.<sup>178</sup>

#### 7.12.9 2-(Naphthalen-1-yl)pyridine (6.19)



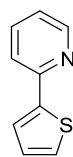
Naphthalen-1-ylboronic acid (1.05 mmol, 0.181 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow oil (90% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.81 (d, *J* = 4.9 Hz, 1H), 8.14 – 8.04 (m, 1H), 7.92 (dd, *J* = 6.0, 2.0 Hz, 2H), 7.88 – 7.79 (m, 1H), 7.66 – 7.43 (m, 5H), 7.35 (dd, *J* = 7.5, 4.9 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.1, 149.3, 138.2, 136.7, 134.0, 131.1, 129.1, 128.4, 127.6, 126.6, 126.0, 125.6, 125.4, 125.2, 122.2. Data in accordance with literature values.<sup>183</sup>

#### 7.12.10 2-(Phenantren-9-yl)pyridine (6.20)



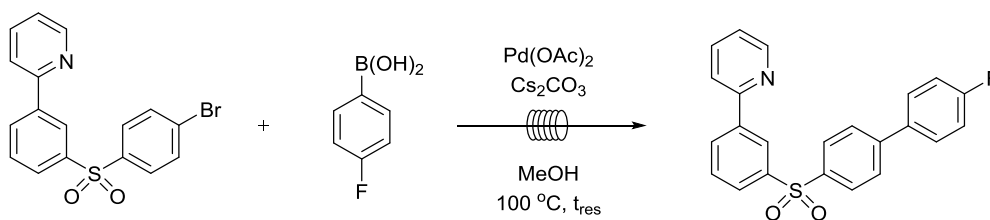
Phenantren-9-ylboronic acid (1.05 mmol, 0.233 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a white solid (83% yield). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.84 (d, *J* = 4.4 Hz, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 7.3 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.88 (s, 1H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.75 – 7.54 (m, 5H), 7.35 (ddd, *J* = 7.5, 4.7, 0.8 Hz, 1H). Data in accordance with literature values.<sup>178</sup>

#### 7.12.11 2-(Thiophen-2-yl)pyridine (6.21)



Thiophen-2-ylboronic acid (1.05 mmol, 0.133 g) was reacted according to the general procedure before purification by flash column chromatography eluting with dichloromethane to give the title compound as a yellow oil (58% yield). **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.60 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.89 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.58 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.37 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.13 (ddd, *J* = 7.3, 4.9, 1.3 Hz, 1H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 153.5, 149.6, 142.1, 136.7, 126.3, 126.2, 123.5, 121.8, 120.3. Data in accordance with literature values.<sup>188</sup>

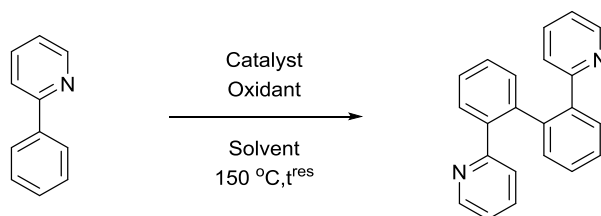
### 7.12.12 2-(3-((4-Fluoro-4'-biphenyl)sulfonyl)phenyl)pyridine (6.23)



4-Fluorophenylboronic acid (1.05 mmol, 0.147 g) 2-(3-((4-bromophenyl)sulfonyl)phenyl)pyridine (1.0 mmol, 0.374 g), cesium carbonate (2.0 mmol, 0.650 g) and Pd(OAc)<sub>2</sub> (0.05 mmol, 1.1 mg) were added to MeOH (50 mL) and stirred until uniform, before being filtered to remove any remaining particulates. The solution was then pumped around the Vapourtec R-2+ module in conjunction with the R-4 reactor heater. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a packed bed of glass beads to a length of 7 cm (volume 2 mL) and a stainless steel coil with a volume of 10 mL, giving a total reaction volume of 12 mL. The reaction column and coil was purged with MeOH (15 mL) and heated to 100 °C prior to introduction of the reagent solution. The temperature was maintained at 100 °C throughout and an additional portion of MeOH (15 mL) was pumped through the reactors after all of the reagent solution had been used. The post-reaction mixture was washed with brine (20 mL), extracted with ethyl acetate (3 × 10 mL), dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography eluting with hexanes/EtOAc (4:1) to give the title compound as an amorphous solid (85% yield). **IR** (neat, cm<sup>-1</sup>)  $\nu$  3067, 2927, 2854, 1732, 1587, 1518, 1485, 1459, 1320, 1301, 1234, 1005, 996, 813, 772, 751, 700, 685, 633. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.61 (d, *J* = 4.5 Hz, 1H), 8.52 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.00 – 7.88 (m, 3H), 7.75 – 7.64 (m, 2H), 7.57 – 7.51 (m, 3H), 7.42 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.20 (td, *J* = 5.0, 2.5 Hz, 1H), 7.04 (t, *J* = 8.5 Hz, 2H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.20 (d, *J* = 248.7 Hz), 155.28, 150.02, 145.21, 142.34, 140.89, 140.15, 137.16, 135.33 (d, *J* = 3.3 Hz), 131.66, 129.93, 129.14 (d, *J* = 8.3 Hz), 128.40, 127.96, 127.90, 126.06, 123.17, 120.80, 116.11 (d, *J* = 21.6 Hz). **HRMS** (ESI) calcd for C<sub>23</sub>H<sub>17</sub>NO<sub>2</sub>SF [M+H]<sup>+</sup>: 390.0964, found: 390.0983.

## 7.13 C-H Functionalisations in Flow

### 7.13.1 General Procedure for formation of 2,2'-di(pyridin-2-yl)-1,1'-biphenyl (6.24) in Flow



2-Phenylpyridine (0.155 g, 1.0 mmol), catalyst and oxidant were added to the required solvent, stirred until uniform and filtered. The reagent solution was pumped around the Vapourtec R-2+ module in conjunction with the R-4 reactor heater for the required residence time. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a packed bed of glass beads to a length of 7 cm (volume 2 mL) and a stainless steel coil with a volume of 10 mL, giving a total reaction volume of 12 mL. The reaction column and coil were purged with solvent (15 mL) and heated to the required temperature prior to introduction of the reagent solution. The temperature was maintained at 150 °C throughout and an additional portion of solvent (15 mL) was pumped through the reactors after all of the catalyst and reagent solutions had been used. The conversion to product was determined by  $^1\text{H}$  NMR.

**Table 7.1** Experimental conditions for oxidative homocoupling in flow

| Entry            | Catalyst   | Oxidant                         | Solvent        | Temp.<br>(°C) | Res. Time<br>(min) | Conversion<br>(%) <sup>[c]</sup> |
|------------------|--|---------------------------------|----------------|---------------|--------------------|----------------------------------|
| 1                | [RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub><br>(2.5 mol%) | TBHP<br>(2 mmol)                | PhCl           | 150           | 200                | 0                                |
| 2                | [RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub><br>(2.5 mol%) | FeCl <sub>3</sub><br>(0.8 mmol) | PhCl           | 150           | 200                | 10                               |
| 3                | Cu(OAc) <sub>2</sub><br>(1 equiv)                                  | I <sub>2</sub><br>(2 mmol)      | MeCN           | 150           | 200                | 12                               |
| 4 <sup>[a]</sup> | Copper coil  | I <sub>2</sub><br>(2 mmol)      | MeCN           | 150           | 200                | 6                                |
| 5 <sup>[b]</sup> | Pd(OAc) <sub>2</sub><br>(5 mol%)                                   | Oxone<br>(Excess)               | <i>i</i> -PrOH | 120           | 20                 | 15 <sup>[d]</sup>                |
| 6 <sup>[b]</sup> | PdCl <sub>2</sub><br>(5 mol%)                                      | Oxone<br>(Excess)               | <i>i</i> -PrOH | 120           | 20                 | 0 <sup>[d]</sup>                 |

[a] A copper reaction coil with a volume of 10 mL was used in place of stainless steel. [b] Oxone was packed into the omnifit reaction column in place of glass beads. [c] Calculated from <sup>1</sup>H NMR spectrum. [d] Alkoxylation product **6.25** was the major product from this reaction.



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## Appendix 1

### Crystallographic Data

**3.33** 2,2'-(4,4'-Ditosyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine

**3.42** 2-(2-Bromo-5-((4-bromophenyl)sulfonyl)-4-methylphenyl)pyridine

**4.32** 1,1'-Di(pyridin-1-yl)-2,2'-binaphthalene

**3.33** 2,2'-(4,4'-Ditosyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine

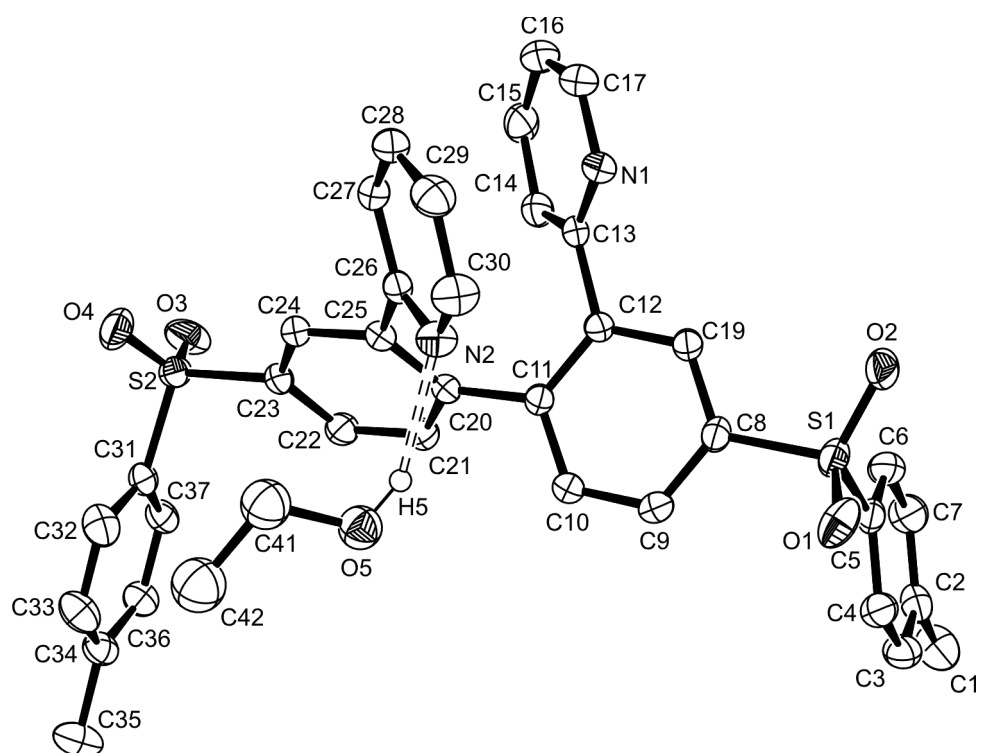


Table A7 Crystal data and structure refinement for h12cgf1.

|                                   |   |
|-----------------------------------|---|
| Identification code               | h12cgf1   |
| Empirical formula                 | C74 H62 N4 O9 S4  |
| Formula weight                    | 1279.52   |
| Temperature                       | 150(2) K  |
| Wavelength                        | 0.71073 Å   |
| Crystal system, space group       | Monoclinic, C 2/c   |
| Unit cell dimensions              | a = 37.8071(6) Å    alpha = 90 deg.<br>b = 10.7146(2) Å    beta = 96.4460(12) deg.<br>c = 15.8811(4) Å    gamma = 90 deg. |
| Volume                            | 6392.6(2) Å <sup>3</sup>  |
| Z, Calculated density             | 4, 1.329 Mg/m <sup>3</sup>  |
| Absorption coefficient            | 0.212 mm <sup>-1</sup>  |
| F(000)                            | 2680  |
| Crystal size                      | 0.55 x 0.50 x 0.38 mm   |
| Theta range for data collection   | 5.01 to 27.46 deg.  |
| Limiting indices                  | -48<=h<=48, -13<=k<=13, -20<=l<=20  |
| Reflections collected / unique    | 45514 / 7237 [R(int) = 0.0625]  |
| Completeness to theta = 27.46     | 98.9 %  |
| Absorption correction             | Semi-empirical from equivalents   |
| Max. and min. transmission        | 0.9238 and 0.8923   |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>   |
| Data / restraints / parameters    | 7237 / 1 / 415  |
| Goodness-of-fit on F <sup>2</sup> | 1.031   |
| Final R indices [I>2sigma(I)]     | R1 = 0.0407, wR2 = 0.0980   |
| R indices (all data)              | R1 = 0.0564, wR2 = 0.1072   |
| Largest diff. peak and hole       | 0.343 and -0.428 e.Å <sup>-3</sup>  |



Table A8 Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf1.

U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|        | x        | y         | z         | U (eq) |
|--------|----------|-----------|-----------|--------|
| S (1)  | 3244 (1) | -4067 (1) | 5441 (1)  | 28 (1) |
| S (2)  | 4189 (1) | 4620 (1)  | 7917 (1)  | 36 (1) |
| O (1)  | 3540 (1) | -4917 (1) | 5505 (1)  | 38 (1) |
| O (2)  | 3028 (1) | -3914 (1) | 4642 (1)  | 41 (1) |
| O (3)  | 3890 (1) | 5386 (1)  | 8076 (1)  | 53 (1) |
| O (4)  | 4443 (1) | 5098 (1)  | 7393 (1)  | 57 (1) |
| N (1)  | 3317 (1) | 598 (1)   | 4190 (1)  | 28 (1) |
| N (2)  | 4222 (1) | 307 (1)   | 5376 (1)  | 30 (1) |
| C (1)  | 2327 (1) | -5387 (2) | 8198 (1)  | 46 (1) |
| C (2)  | 2550 (1) | -5085 (2) | 7496 (1)  | 31 (1) |
| C (3)  | 2885 (1) | -5605 (2) | 7486 (1)  | 33 (1) |
| C (4)  | 3096 (1) | -5319 (2) | 6853 (1)  | 30 (1) |
| C (5)  | 2967 (1) | -4496 (2) | 6216 (1)  | 25 (1) |
| C (6)  | 2632 (1) | -3966 (2) | 6210 (1)  | 34 (1) |
| C (7)  | 2427 (1) | -4263 (2) | 6847 (1)  | 37 (1) |
| C (8)  | 3400 (1) | -2577 (1) | 5779 (1)  | 24 (1) |
| C (9)  | 3614 (1) | -2467 (2) | 6547 (1)  | 29 (1) |
| C (10) | 3723 (1) | -1289 (2) | 6818 (1)  | 28 (1) |
| C (11) | 3624 (1) | -220 (1)  | 6343 (1)  | 23 (1) |
| C (12) | 3408 (1) | -346 (1)  | 5566 (1)  | 21 (1) |
| C (13) | 3281 (1) | 731 (1)   | 5020 (1)  | 23 (1) |
| C (14) | 3122 (1) | 1773 (2)  | 5340 (1)  | 30 (1) |
| C (15) | 2998 (1) | 2720 (2)  | 4793 (1)  | 38 (1) |
| C (16) | 3046 (1) | 2614 (2)  | 3945 (1)  | 42 (1) |
| C (17) | 3204 (1) | 1549 (2)  | 3681 (1)  | 37 (1) |
| C (19) | 3301 (1) | -1536 (1) | 5292 (1)  | 23 (1) |
| C (20) | 3759 (1) | 998 (1)   | 6701 (1)  | 23 (1) |
| C (21) | 3683 (1) | 1326 (2)  | 7514 (1)  | 27 (1) |
| C (22) | 3811 (1) | 2428 (2)  | 7894 (1)  | 30 (1) |
| C (23) | 4018 (1) | 3210 (2)  | 7451 (1)  | 27 (1) |
| C (24) | 4095 (1) | 2911 (2)  | 6645 (1)  | 26 (1) |
| C (25) | 3970 (1) | 1798 (2)  | 6264 (1)  | 24 (1) |
| C (26) | 4083 (1) | 1453 (2)  | 5426 (1)  | 24 (1) |
| C (27) | 4051 (1) | 2292 (2)  | 4754 (1)  | 27 (1) |
| C (28) | 4165 (1) | 1921 (2)  | 3993 (1)  | 31 (1) |
| C (29) | 4306 (1) | 745 (2)   | 3929 (1)  | 34 (1) |
| C (30) | 4328 (1) | -29 (2)   | 4632 (1)  | 36 (1) |
| C (31) | 4412 (1) | 4162 (2)  | 8901 (1)  | 27 (1) |
| C (32) | 4760 (1) | 3737 (2)  | 8955 (1)  | 36 (1) |
| C (33) | 4924 (1) | 3336 (2)  | 9732 (1)  | 38 (1) |
| C (34) | 4745 (1) | 3349 (2)  | 10451 (1) | 31 (1) |
| C (35) | 4922 (1) | 2909 (2)  | 11294 (1) | 47 (1) |
| C (36) | 4398 (1) | 3787 (2)  | 10377 (1) | 31 (1) |
| C (37) | 4229 (1) | 4194 (2)  | 9606 (1)  | 29 (1) |
| O (5)  | 4597 (1) | -188 (3)  | 7038 (2)  | 40 (1) |
| C (41) | 4871 (2) | 700 (5)   | 6955 (4)  | 51 (1) |
| C (42) | 5121 (2) | 811 (6)   | 7753 (4)  | 61 (2) |

Table A9 Bond lengths [Å] for h12cgf1.

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|             |            |
|-------------|------------|
| S(1)-O(1)   | 1.4375(14) |
| S(1)-O(2)   | 1.4403(13) |
| S(1)-C(5)   | 1.7625(16) |
| S(1)-C(8)   | 1.7647(16) |
| S(2)-O(4)   | 1.4340(15) |
| S(2)-O(3)   | 1.4411(16) |
| S(2)-C(31)  | 1.7588(17) |
| S(2)-C(23)  | 1.7733(16) |
| N(1)-C(17)  | 1.339(2)   |
| N(1)-C(13)  | 1.347(2)   |
| N(2)-C(30)  | 1.338(2)   |
| N(2)-C(26)  | 1.342(2)   |
| C(1)-C(2)   | 1.506(2)   |
| C(1)-H(1A)  | 0.9800     |
| C(1)-H(1B)  | 0.9800     |
| C(1)-H(1C)  | 0.9800     |
| C(2)-C(3)   | 1.384(3)   |
| C(2)-C(7)   | 1.395(3)   |
| C(3)-C(4)   | 1.386(2)   |
| C(3)-H(3)   | 0.9500     |
| C(4)-C(5)   | 1.388(2)   |
| C(4)-H(4)   | 0.9500     |
| C(5)-C(6)   | 1.387(2)   |
| C(6)-C(7)   | 1.379(3)   |
| C(6)-H(6)   | 0.9500     |
| C(7)-H(7)   | 0.9500     |
| C(8)-C(19)  | 1.386(2)   |
| C(8)-C(9)   | 1.389(2)   |
| C(9)-C(10)  | 1.382(2)   |
| C(9)-H(9)   | 0.9500     |
| C(10)-C(11) | 1.399(2)   |
| C(10)-H(10) | 0.9500     |
| C(11)-C(12) | 1.407(2)   |
| C(11)-C(20) | 1.490(2)   |
| C(12)-C(19) | 1.394(2)   |
| C(12)-C(13) | 1.491(2)   |
| C(13)-C(14) | 1.391(2)   |
| C(14)-C(15) | 1.383(2)   |
| C(14)-H(14) | 0.9500     |
| C(15)-C(16) | 1.385(3)   |
| C(15)-H(15) | 0.9500     |
| C(16)-C(17) | 1.375(3)   |
| C(16)-H(16) | 0.9500     |
| C(17)-H(17) | 0.9500     |
| C(19)-H(19) | 0.9500     |
| C(20)-C(21) | 1.399(2)   |
| C(20)-C(25) | 1.407(2)   |
| C(21)-C(22) | 1.388(2)   |
| C(21)-H(21) | 0.9500     |
| C(22)-C(23) | 1.389(2)   |
| C(22)-H(22) | 0.9500     |
| C(23)-C(24) | 1.383(2)   |
| C(24)-C(25) | 1.395(2)   |
| C(24)-H(24) | 0.9500     |
| C(25)-C(26) | 1.489(2)   |
| C(26)-C(27) | 1.390(2)   |
| C(27)-C(28) | 1.387(2)   |
| C(27)-H(27) | 0.9500     |
| C(28)-C(29) | 1.375(3)   |
| C(28)-H(28) | 0.9500     |

|              |          |
|--------------|----------|
| C(29)-C(30)  | 1.387(3) |
| C(29)-H(29)  | 0.9500   |
| C(30)-H(30)  | 0.9500   |
| C(31)-C(37)  | 1.380(2) |
| C(31)-C(32)  | 1.389(3) |
| C(32)-C(33)  | 1.385(3) |
| C(32)-H(32)  | 0.9500   |
| C(33)-C(34)  | 1.391(3) |
| C(33)-H(33)  | 0.9500   |
| C(34)-C(36)  | 1.386(2) |
| C(34)-C(35)  | 1.505(2) |
| C(35)-H(35A) | 0.9800   |
| C(35)-H(35B) | 0.9800   |
| C(35)-H(35C) | 0.9800   |
| C(36)-C(37)  | 1.385(2) |
| C(36)-H(36)  | 0.9500   |
| C(37)-H(37)  | 0.9500   |
| O(5)-C(41)   | 1.423(6) |
| O(5)-H(5)    | 0.88(2)  |
| C(41)-C(42)  | 1.496(8) |
| C(41)-H(41A) | 0.9900   |
| C(41)-H(41B) | 0.9900   |
| C(42)-H(42A) | 0.9800   |
| C(42)-H(42B) | 0.9800   |
| C(42)-H(42C) | 0.9800   |

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Table A10 Bond angles [deg] for h12cgf1.

|                  |            |
|------------------|------------|
| O(1)-S(1)-O(2)   | 119.58(8)  |
| O(1)-S(1)-C(5)   | 107.70(8)  |
| O(2)-S(1)-C(5)   | 108.87(8)  |
| O(1)-S(1)-C(8)   | 108.67(8)  |
| O(2)-S(1)-C(8)   | 107.61(8)  |
| C(5)-S(1)-C(8)   | 103.20(7)  |
| O(4)-S(2)-O(3)   | 119.17(10) |
| O(4)-S(2)-C(31)  | 109.32(9)  |
| O(3)-S(2)-C(31)  | 108.07(8)  |
| O(4)-S(2)-C(23)  | 107.41(8)  |
| O(3)-S(2)-C(23)  | 107.49(8)  |
| C(31)-S(2)-C(23) | 104.39(8)  |
| C(17)-N(1)-C(13) | 116.73(15) |
| C(30)-N(2)-C(26) | 117.19(15) |
| C(2)-C(1)-H(1A)  | 109.5      |
| C(2)-C(1)-H(1B)  | 109.5      |
| H(1A)-C(1)-H(1B) | 109.5      |
| C(2)-C(1)-H(1C)  | 109.5      |
| H(1A)-C(1)-H(1C) | 109.5      |
| H(1B)-C(1)-H(1C) | 109.5      |
| C(3)-C(2)-C(7)   | 118.33(16) |
| C(3)-C(2)-C(1)   | 120.68(17) |
| C(7)-C(2)-C(1)   | 120.99(17) |
| C(2)-C(3)-C(4)   | 121.38(16) |

|                   |            |
|-------------------|------------|
| C(2)-C(3)-H(3)    | 119.3      |
| C(4)-C(3)-H(3)    | 119.3      |
| C(3)-C(4)-C(5)    | 119.09(16) |
| C(3)-C(4)-H(4)    | 120.5      |
| C(5)-C(4)-H(4)    | 120.5      |
| C(6)-C(5)-C(4)    | 120.66(15) |
| C(6)-C(5)-S(1)    | 120.04(13) |
| C(4)-C(5)-S(1)    | 119.22(13) |
| C(7)-C(6)-C(5)    | 119.21(16) |
| C(7)-C(6)-H(6)    | 120.4      |
| C(5)-C(6)-H(6)    | 120.4      |
| C(6)-C(7)-C(2)    | 121.34(17) |
| C(6)-C(7)-H(7)    | 119.3      |
| C(2)-C(7)-H(7)    | 119.3      |
| C(19)-C(8)-C(9)   | 121.09(14) |
| C(19)-C(8)-S(1)   | 119.84(12) |
| C(9)-C(8)-S(1)    | 119.04(12) |
| C(10)-C(9)-C(8)   | 118.30(15) |
| C(10)-C(9)-H(9)   | 120.9      |
| C(8)-C(9)-H(9)    | 120.9      |
| C(9)-C(10)-C(11)  | 121.91(15) |
| C(9)-C(10)-H(10)  | 119.0      |
| C(11)-C(10)-H(10) | 119.0      |
| C(10)-C(11)-C(12) | 119.15(14) |
| C(10)-C(11)-C(20) | 116.91(13) |
| C(12)-C(11)-C(20) | 123.94(14) |
| C(19)-C(12)-C(11) | 118.84(14) |
| C(19)-C(12)-C(13) | 117.53(13) |
| C(11)-C(12)-C(13) | 123.62(13) |
| N(1)-C(13)-C(14)  | 122.52(15) |
| N(1)-C(13)-C(12)  | 115.24(14) |
| C(14)-C(13)-C(12) | 122.17(14) |
| C(15)-C(14)-C(13) | 119.28(16) |
| C(15)-C(14)-H(14) | 120.4      |
| C(13)-C(14)-H(14) | 120.4      |
| C(14)-C(15)-C(16) | 118.59(17) |
| C(14)-C(15)-H(15) | 120.7      |
| C(16)-C(15)-H(15) | 120.7      |
| C(17)-C(16)-C(15) | 118.25(17) |
| C(17)-C(16)-H(16) | 120.9      |
| C(15)-C(16)-H(16) | 120.9      |
| N(1)-C(17)-C(16)  | 124.55(17) |
| N(1)-C(17)-H(17)  | 117.7      |
| C(16)-C(17)-H(17) | 117.7      |
| C(8)-C(19)-C(12)  | 120.70(14) |
| C(8)-C(19)-H(19)  | 119.6      |
| C(12)-C(19)-H(19) | 119.6      |
| C(21)-C(20)-C(25) | 119.30(14) |
| C(21)-C(20)-C(11) | 118.42(14) |
| C(25)-C(20)-C(11) | 122.23(14) |
| C(22)-C(21)-C(20) | 121.17(15) |
| C(22)-C(21)-H(21) | 119.4      |
| C(20)-C(21)-H(21) | 119.4      |
| C(21)-C(22)-C(23) | 118.78(15) |
| C(21)-C(22)-H(22) | 120.6      |
| C(23)-C(22)-H(22) | 120.6      |
| C(24)-C(23)-C(22) | 121.18(15) |
| C(24)-C(23)-S(2)  | 118.61(12) |
| C(22)-C(23)-S(2)  | 120.20(13) |
| C(23)-C(24)-C(25) | 120.27(15) |
| C(23)-C(24)-H(24) | 119.9      |
| C(25)-C(24)-H(24) | 119.9      |
| C(24)-C(25)-C(20) | 119.28(14) |

|                          |             |
|--------------------------|-------------|
| C (24) -C (25) -C (26)   | 118.84 (14) |
| C (20) -C (25) -C (26)   | 121.77 (14) |
| N (2) -C (26) -C (27)    | 123.16 (15) |
| N (2) -C (26) -C (25)    | 115.77 (14) |
| C (27) -C (26) -C (25)   | 121.06 (15) |
| C (28) -C (27) -C (26)   | 118.32 (16) |
| C (28) -C (27) -H (27)   | 120.8       |
| C (26) -C (27) -H (27)   | 120.8       |
| C (29) -C (28) -C (27)   | 119.23 (16) |
| C (29) -C (28) -H (28)   | 120.4       |
| C (27) -C (28) -H (28)   | 120.4       |
| C (28) -C (29) -C (30)   | 118.50 (16) |
| C (28) -C (29) -H (29)   | 120.7       |
| C (30) -C (29) -H (29)   | 120.7       |
| N (2) -C (30) -C (29)    | 123.58 (17) |
| N (2) -C (30) -H (30)    | 118.2       |
| C (29) -C (30) -H (30)   | 118.2       |
| C (37) -C (31) -C (32)   | 121.04 (16) |
| C (37) -C (31) -S (2)    | 118.73 (13) |
| C (32) -C (31) -S (2)    | 120.19 (13) |
| C (33) -C (32) -C (31)   | 118.79 (16) |
| C (33) -C (32) -H (32)   | 120.6       |
| C (31) -C (32) -H (32)   | 120.6       |
| C (32) -C (33) -C (34)   | 121.31 (17) |
| C (32) -C (33) -H (33)   | 119.3       |
| C (34) -C (33) -H (33)   | 119.3       |
| C (36) -C (34) -C (33)   | 118.46 (16) |
| C (36) -C (34) -C (35)   | 120.32 (16) |
| C (33) -C (34) -C (35)   | 121.22 (17) |
| C (34) -C (35) -H (35A)  | 109.5       |
| C (34) -C (35) -H (35B)  | 109.5       |
| H (35A) -C (35) -H (35B) | 109.5       |
| C (34) -C (35) -H (35C)  | 109.5       |
| H (35A) -C (35) -H (35C) | 109.5       |
| H (35B) -C (35) -H (35C) | 109.5       |
| C (37) -C (36) -C (34)   | 121.22 (16) |
| C (37) -C (36) -H (36)   | 119.4       |
| C (34) -C (36) -H (36)   | 119.4       |
| C (31) -C (37) -C (36)   | 119.17 (16) |
| C (31) -C (37) -H (37)   | 120.4       |
| C (36) -C (37) -H (37)   | 120.4       |
| C (41) -O (5) -H (5)     | 115 (6)     |
| O (5) -C (41) -C (42)    | 111.8 (5)   |
| O (5) -C (41) -H (41A)   | 109.3       |
| C (42) -C (41) -H (41A)  | 109.3       |
| O (5) -C (41) -H (41B)   | 109.3       |
| C (42) -C (41) -H (41B)  | 109.3       |
| H (41A) -C (41) -H (41B) | 107.9       |
| C (41) -C (42) -H (42A)  | 109.5       |
| C (41) -C (42) -H (42B)  | 109.5       |
| H (42A) -C (42) -H (42B) | 109.5       |
| C (41) -C (42) -H (42C)  | 109.5       |
| H (42A) -C (42) -H (42C) | 109.5       |
| H (42B) -C (42) -H (42C) | 109.5       |

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Table A11 Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf1.

The anisotropic displacement factor exponent takes the form:

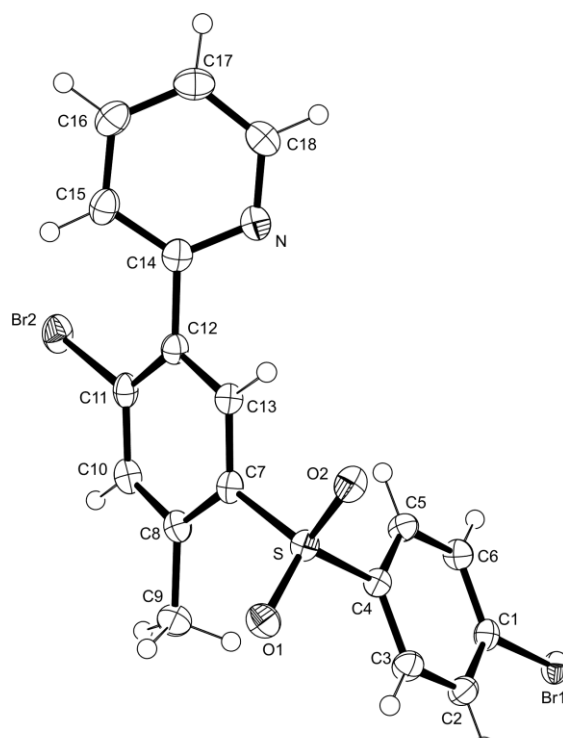
$$-2 \pi^2 [ h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12} ]$$

|        | U11    | U22    | U33    | U23    | U13     | U12     |
|--------|--------|--------|--------|--------|---------|---------|
| S (1)  | 39 (1) | 21 (1) | 26 (1) | -2 (1) | 7 (1)   | -8 (1)  |
| S (2)  | 57 (1) | 23 (1) | 25 (1) | 0 (1)  | -11 (1) | -11 (1) |
| O (1)  | 46 (1) | 24 (1) | 48 (1) | -3 (1) | 23 (1)  | -2 (1)  |
| O (2)  | 63 (1) | 34 (1) | 24 (1) | -3 (1) | 0 (1)   | -19 (1) |
| O (3)  | 77 (1) | 27 (1) | 47 (1) | -8 (1) | -27 (1) | 14 (1)  |
| O (4)  | 91 (1) | 50 (1) | 27 (1) | 6 (1)  | -7 (1)  | -45 (1) |
| N (1)  | 32 (1) | 29 (1) | 23 (1) | 3 (1)  | -2 (1)  | -4 (1)  |
| N (2)  | 32 (1) | 31 (1) | 28 (1) | 2 (1)  | 3 (1)   | 4 (1)   |
| C (1)  | 37 (1) | 67 (1) | 37 (1) | -1 (1) | 11 (1)  | -8 (1)  |
| C (2)  | 29 (1) | 37 (1) | 28 (1) | -5 (1) | 3 (1)   | -8 (1)  |
| C (3)  | 34 (1) | 37 (1) | 28 (1) | 6 (1)  | 2 (1)   | -2 (1)  |
| C (4)  | 29 (1) | 29 (1) | 32 (1) | 4 (1)  | 4 (1)   | 1 (1)   |
| C (5)  | 29 (1) | 21 (1) | 25 (1) | -2 (1) | 3 (1)   | -7 (1)  |
| C (6)  | 30 (1) | 33 (1) | 36 (1) | 7 (1)  | -2 (1)  | -1 (1)  |
| C (7)  | 25 (1) | 41 (1) | 44 (1) | 3 (1)  | 4 (1)   | 0 (1)   |
| C (8)  | 28 (1) | 20 (1) | 25 (1) | -2 (1) | 5 (1)   | -5 (1)  |
| C (9)  | 34 (1) | 24 (1) | 27 (1) | 5 (1)  | 0 (1)   | -1 (1)  |
| C (10) | 32 (1) | 26 (1) | 23 (1) | 3 (1)  | -4 (1)  | -4 (1)  |
| C (11) | 24 (1) | 22 (1) | 21 (1) | 1 (1)  | 2 (1)   | -4 (1)  |
| C (12) | 21 (1) | 22 (1) | 20 (1) | 1 (1)  | 2 (1)   | -1 (1)  |
| C (13) | 22 (1) | 22 (1) | 24 (1) | 1 (1)  | -3 (1)  | -5 (1)  |
| C (14) | 32 (1) | 25 (1) | 30 (1) | -2 (1) | -2 (1)  | -1 (1)  |
| C (15) | 41 (1) | 23 (1) | 48 (1) | -2 (1) | -8 (1)  | 2 (1)   |
| C (16) | 51 (1) | 30 (1) | 42 (1) | 12 (1) | -13 (1) | -2 (1)  |
| C (17) | 46 (1) | 35 (1) | 27 (1) | 7 (1)  | -5 (1)  | -5 (1)  |
| C (19) | 25 (1) | 23 (1) | 21 (1) | 0 (1)  | 1 (1)   | -4 (1)  |
| C (20) | 24 (1) | 22 (1) | 22 (1) | 1 (1)  | -3 (1)  | -1 (1)  |
| C (21) | 32 (1) | 26 (1) | 23 (1) | 1 (1)  | 2 (1)   | -6 (1)  |
| C (22) | 40 (1) | 29 (1) | 21 (1) | -2 (1) | 0 (1)   | -3 (1)  |
| C (23) | 33 (1) | 22 (1) | 24 (1) | -1 (1) | -6 (1)  | -4 (1)  |
| C (24) | 27 (1) | 24 (1) | 24 (1) | 2 (1)  | -2 (1)  | -5 (1)  |
| C (25) | 24 (1) | 24 (1) | 22 (1) | 1 (1)  | -2 (1)  | -1 (1)  |
| C (26) | 23 (1) | 26 (1) | 23 (1) | 0 (1)  | 0 (1)   | -5 (1)  |
| C (27) | 31 (1) | 24 (1) | 26 (1) | 1 (1)  | 0 (1)   | -6 (1)  |
| C (28) | 34 (1) | 33 (1) | 23 (1) | 5 (1)  | 0 (1)   | -6 (1)  |
| C (29) | 36 (1) | 42 (1) | 26 (1) | -2 (1) | 6 (1)   | 0 (1)   |
| C (30) | 40 (1) | 35 (1) | 33 (1) | 0 (1)  | 8 (1)   | 7 (1)   |
| C (31) | 34 (1) | 25 (1) | 22 (1) | -4 (1) | -3 (1)  | -6 (1)  |
| C (32) | 33 (1) | 46 (1) | 28 (1) | -7 (1) | 7 (1)   | -5 (1)  |
| C (33) | 28 (1) | 50 (1) | 37 (1) | -8 (1) | 0 (1)   | 6 (1)   |
| C (34) | 35 (1) | 30 (1) | 26 (1) | -4 (1) | -2 (1)  | 2 (1)   |
| C (35) | 51 (1) | 55 (1) | 34 (1) | 2 (1)  | -7 (1)  | 15 (1)  |
| C (36) | 33 (1) | 34 (1) | 24 (1) | -5 (1) | 4 (1)   | 2 (1)   |
| C (37) | 28 (1) | 30 (1) | 28 (1) | -6 (1) | -1 (1)  | 3 (1)   |

Table A12 Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf1.

|        | x         | y         | z         | U(eq)    |
|--------|-----------|-----------|-----------|----------|
| H(1A)  | 2279      | -6286     | 8200      | 69       |
| H(1B)  | 2101      | -4931     | 8106      | 69       |
| H(1C)  | 2455      | -5142     | 8743      | 69       |
| H(3)   | 2971      | -6169     | 7923      | 40       |
| H(4)   | 3325      | -5682     | 6855      | 36       |
| H(6)   | 2545      | -3406     | 5771      | 40       |
| H(7)   | 2198      | -3900     | 6845      | 44       |
| H(9)   | 3683      | -3184     | 6877      | 34       |
| H(10)  | 3869      | -1202     | 7341      | 33       |
| H(14)  | 3100      | 1834      | 5929      | 35       |
| H(15)  | 2882      | 3427      | 4996      | 46       |
| H(16)  | 2972      | 3261      | 3555      | 51       |
| H(17)  | 3235      | 1481      | 3097      | 44       |
| H(19)  | 3158      | -1635     | 4764      | 28       |
| H(21)  | 3542      | 784       | 7812      | 32       |
| H(22)  | 3758      | 2644      | 8446      | 36       |
| H(24)  | 4233      | 3465      | 6349      | 31       |
| H(27)  | 3953      | 3099      | 4815      | 33       |
| H(28)  | 4147      | 2473      | 3522      | 37       |
| H(29)  | 4385      | 469       | 3413      | 41       |
| H(30)  | 4423      | -843      | 4583      | 43       |
| H(32)  | 4885      | 3722      | 8467      | 43       |
| H(33)  | 5162      | 3046      | 9775      | 46       |
| H(35A) | 5159      | 3289      | 11403     | 71       |
| H(35B) | 4946      | 1998      | 11286     | 71       |
| H(35C) | 4777      | 3152      | 11742     | 71       |
| H(36)  | 4273      | 3809      | 10863     | 37       |
| H(37)  | 3991      | 4492      | 9563      | 35       |
| H(5)   | 4432 (18) | -220 (90) | 6610 (40) | 170 (40) |
| H(41A) | 4762      | 1525      | 6812      | 61       |
| H(41B) | 5007      | 447       | 6485      | 61       |
| H(42A) | 5304      | 1433      | 7674      | 92       |
| H(42B) | 5234      | 1         | 7889      | 92       |
| H(42C) | 4988      | 1072      | 8218      | 92       |

**3.42** 2-(2-Bromo-5-((4-bromophenyl)sulfonyl)-4-methylphenyl)pyridine



CCDC 944822 contains the crystallographic data for compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



Table A1 Crystal data and structure refinement for k12cgf3.

|                                   |   |
|-----------------------------------|---|
| Identification code               | k12cgf3   |
| Empirical formula                 | C18 H13 Br2 N O2 S  |
| Formula weight                    | 467.17  |
| Temperature                       | 150(2) K  |
| Wavelength                        | 0.71073 Å   |
| Crystal system, space group       | Orthorhombic, $P 2_1 n$   |
| Unit cell dimensions              | a = 7.74360(10) Å $\alpha$ = 90 deg.<br>b = 12.0742(2) Å $\beta$ = 90 deg.<br>c = 18.1276(2) Å $\gamma$ = 90 deg. |
| Volume                            | 1694.89(4) Å <sup>3</sup>   |
| Z, Calculated density             | 4, 1.831 Mg/m <sup>3</sup>  |
| Absorption coefficient            | 4.916 mm <sup>-1</sup>  |
| F(000)                            | 920   |
| Crystal size                      | 0.30 x 0.20 x 0.15 mm   |
| Theta range for data collection   | 3.32 to 30.02 deg.  |
| Limiting indices                  | $-9 \leq h \leq 10$ , $-16 \leq k \leq 16$ , $-25 \leq l \leq 23$   |
| Reflections collected / unique    | 36829 / 4717 [R(int) = 0.0770]  |
| Completeness to theta = 30.02     | 99.8 %  |
| Absorption correction             | Semi-empirical from equivalents   |
| Max. and min. transmission        | 0.5259 and 0.3202   |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>   |
| Data / restraints / parameters    | 4717 / 1 / 218  |
| Goodness-of-fit on F <sup>2</sup> | 1.019   |
| Final R indices [I > 2sigma(I)]   | R1 = 0.0333, wR2 = 0.0767   |
| R indices (all data)              | R1 = 0.0414, wR2 = 0.0809   |
| Absolute structure parameter      | 0.001(7)  |
| Largest diff. peak and hole       | 0.355 and -0.764 e.Å <sup>-3</sup>  |

Table A2 Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for k12cgf3.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

|        | x         | y         | z        | U (eq) |
|--------|-----------|-----------|----------|--------|
| Br (1) | -1345 (1) | 6529 (1)  | 7622 (1) | 26 (1) |
| Br (2) | 1680 (1)  | 1051 (1)  | 3668 (1) | 33 (1) |
| S      | 4905 (1)  | 3490 (1)  | 6488 (1) | 20 (1) |
| O (1)  | 6341 (3)  | 4194 (2)  | 6300 (1) | 28 (1) |
| O (2)  | 5180 (3)  | 2640 (2)  | 7035 (1) | 25 (1) |
| C (1)  | 527 (4)   | 5642 (3)  | 7300 (2) | 22 (1) |
| C (2)  | 2184 (4)  | 6064 (3)  | 7294 (2) | 25 (1) |
| C (3)  | 3532 (5)  | 5416 (3)  | 7042 (2) | 25 (1) |
| C (4)  | 3185 (4)  | 4346 (2)  | 6793 (2) | 20 (1) |
| C (5)  | 1518 (4)  | 3920 (2)  | 6799 (2) | 23 (1) |
| C (6)  | 168 (4)   | 4571 (3)  | 7057 (2) | 23 (1) |
| C (7)  | 4057 (3)  | 2849 (3)  | 5687 (2) | 21 (1) |
| C (8)  | 3682 (5)  | 3449 (2)  | 5045 (2) | 22 (1) |
| C (9)  | 4036 (4)  | 4684 (3)  | 4959 (2) | 28 (1) |
| C (10) | 2961 (4)  | 2873 (3)  | 4464 (2) | 25 (1) |
| C (11) | 2687 (4)  | 1724 (3)  | 4505 (2) | 23 (1) |
| C (12) | 3093 (4)  | 1120 (3)  | 5138 (2) | 22 (1) |
| C (13) | 3769 (4)  | 1714 (2)  | 5733 (2) | 21 (1) |
| C (14) | 2850 (4)  | -98 (3)   | 5238 (2) | 24 (1) |
| C (15) | 3447 (5)  | -871 (3)  | 4730 (2) | 28 (1) |
| C (16) | 3263 (4)  | -1995 (3) | 4894 (2) | 31 (1) |
| C (17) | 2474 (5)  | -2294 (3) | 5549 (2) | 32 (1) |
| C (18) | 1911 (5)  | -1465 (3) | 6017 (2) | 30 (1) |
| N      | 2096 (4)  | -380 (2)  | 5877 (2) | 26 (1) |

Table A3 Bond lengths [Å] for k12cgf3.

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|                |           |
|----------------|-----------|
| Br (1) -C (1)  | 1.895 (3) |
| Br (2) -C (11) | 1.891 (3) |
| S-O (1)        | 1.441 (2) |
| S-O (2)        | 1.443 (2) |
| S-C (7)        | 1.772 (3) |
| S-C (4)        | 1.773 (3) |
| C (1) -C (2)   | 1.381 (5) |
| C (1) -C (6)   | 1.394 (4) |
| C (2) -C (3)   | 1.382 (5) |
| C (2) -H (2)   | 0.9500    |
| C (3) -C (4)   | 1.395 (4) |
| C (3) -H (3)   | 0.9500    |
| C (4) -C (5)   | 1.390 (5) |
| C (5) -C (6)   | 1.388 (4) |
| C (5) -H (5)   | 0.9500    |
| C (6) -H (6)   | 0.9500    |
| C (7) -C (13)  | 1.391 (4) |
| C (7) -C (8)   | 1.401 (4) |
| C (8) -C (10)  | 1.381 (4) |
| C (8) -C (9)   | 1.524 (4) |
| C (9) -H (9A)  | 0.9800    |
| C (9) -H (9B)  | 0.9800    |
| C (9) -H (9C)  | 0.9800    |
| C (10) -C (11) | 1.405 (5) |
| C (10) -H (10) | 0.9500    |
| C (11) -C (12) | 1.395 (4) |
| C (12) -C (13) | 1.397 (4) |
| C (12) -C (14) | 1.495 (4) |
| C (13) -H (13) | 0.9500    |
| C (14) -N      | 1.341 (4) |
| C (14) -C (15) | 1.390 (4) |
| C (15) -C (16) | 1.396 (5) |
| C (15) -H (15) | 0.9500    |
| C (16) -C (17) | 1.384 (5) |
| C (16) -H (16) | 0.9500    |
| C (17) -C (18) | 1.382 (5) |
| C (17) -H (17) | 0.9500    |
| C (18) -N      | 1.342 (4) |
| C (18) -H (18) | 0.9500    |

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Table A4 Bond lengths [Å] and angles [deg] for k12cgf3.

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|                      |             |
|----------------------|-------------|
| O (1) -S-O (2)       | 117.92 (14) |
| O (1) -S-C (7)       | 110.46 (14) |
| O (2) -S-C (7)       | 107.85 (14) |
| O (1) -S-C (4)       | 108.09 (14) |
| O (2) -S-C (4)       | 108.15 (14) |
| C (7) -S-C (4)       | 103.38 (13) |
| C (2) -C (1) -C (6)  | 121.6 (3)   |
| C (2) -C (1) -Br (1) | 120.3 (2)   |
| C (6) -C (1) -Br (1) | 118.0 (2)   |
| C (1) -C (2) -C (3)  | 119.7 (3)   |

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|                        |           |
|------------------------|-----------|
| C (1) -C (2) -H (2)    | 120.1     |
| C (3) -C (2) -H (2)    | 120.1     |
| C (2) -C (3) -C (4)    | 119.1 (3) |
| C (2) -C (3) -H (3)    | 120.5     |
| C (4) -C (3) -H (3)    | 120.5     |
| C (5) -C (4) -C (3)    | 121.3 (3) |
| C (5) -C (4) -S        | 119.0 (2) |
| C (3) -C (4) -S        | 119.7 (2) |
| C (6) -C (5) -C (4)    | 119.5 (3) |
| C (6) -C (5) -H (5)    | 120.2     |
| C (4) -C (5) -H (5)    | 120.2     |
| C (5) -C (6) -C (1)    | 118.8 (3) |
| C (5) -C (6) -H (6)    | 120.6     |
| C (1) -C (6) -H (6)    | 120.6     |
| C (13) -C (7) -C (8)   | 121.8 (3) |
| C (13) -C (7) -S       | 116.1 (2) |
| C (8) -C (7) -S        | 122.1 (2) |
| C (10) -C (8) -C (7)   | 117.2 (3) |
| C (10) -C (8) -C (9)   | 119.1 (3) |
| C (7) -C (8) -C (9)    | 123.7 (3) |
| C (8) -C (9) -H (9A)   | 109.5     |
| C (8) -C (9) -H (9B)   | 109.5     |
| H (9A) -C (9) -H (9B)  | 109.5     |
| C (8) -C (9) -H (9C)   | 109.5     |
| H (9A) -C (9) -H (9C)  | 109.5     |
| H (9B) -C (9) -H (9C)  | 109.5     |
| C (8) -C (10) -C (11)  | 121.2 (3) |
| C (8) -C (10) -H (10)  | 119.4     |
| C (11) -C (10) -H (10) | 119.4     |
| C (12) -C (11) -C (10) | 121.7 (3) |
| C (12) -C (11) -Br (2) | 121.9 (2) |
| C (10) -C (11) -Br (2) | 116.3 (2) |
| C (11) -C (12) -C (13) | 116.8 (3) |
| C (11) -C (12) -C (14) | 125.9 (3) |
| C (13) -C (12) -C (14) | 117.3 (3) |
| C (7) -C (13) -C (12)  | 121.2 (3) |
| C (7) -C (13) -H (13)  | 119.4     |
| C (12) -C (13) -H (13) | 119.4     |
| N-C (14) -C (15)       | 123.2 (3) |
| N-C (14) -C (12)       | 114.2 (3) |
| C (15) -C (14) -C (12) | 122.6 (3) |
| C (14) -C (15) -C (16) | 118.5 (3) |
| C (14) -C (15) -H (15) | 120.8     |
| C (16) -C (15) -H (15) | 120.8     |
| C (17) -C (16) -C (15) | 118.8 (3) |
| C (17) -C (16) -H (16) | 120.6     |
| C (15) -C (16) -H (16) | 120.6     |
| C (18) -C (17) -C (16) | 118.5 (3) |
| C (18) -C (17) -H (17) | 120.8     |
| C (16) -C (17) -H (17) | 120.8     |
| N-C (18) -C (17)       | 123.9 (3) |
| N-C (18) -H (18)       | 118.1     |
| C (17) -C (18) -H (18) | 118.1     |
| C (14) -N-C (18)       | 117.2 (3) |

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Table A5 Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for k12cgf3.

The anisotropic displacement factor exponent takes the form:  
 $-2 \pi^2 [ h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12} ]$

|        | U11    | U22    | U33    | U23    | U13    | U12    |
|--------|--------|--------|--------|--------|--------|--------|
| Br (1) | 25 (1) | 28 (1) | 26 (1) | -2 (1) | 3 (1)  | 7 (1)  |
| Br (2) | 33 (1) | 46 (1) | 21 (1) | -3 (1) | -4 (1) | -5 (1) |
| S      | 15 (1) | 24 (1) | 21 (1) | -1 (1) | -2 (1) | 2 (1)  |
| O (1)  | 16 (1) | 32 (1) | 34 (1) | -1 (1) | 3 (1)  | -3 (1) |
| O (2)  | 24 (1) | 29 (1) | 22 (1) | -1 (1) | -7 (1) | 6 (1)  |
| C (1)  | 21 (2) | 26 (1) | 19 (1) | -1 (1) | 0 (1)  | 4 (1)  |
| C (2)  | 25 (2) | 23 (2) | 26 (2) | -4 (1) | 1 (1)  | 0 (1)  |
| C (3)  | 20 (1) | 27 (1) | 27 (2) | -5 (1) | -1 (1) | -4 (1) |
| C (4)  | 20 (1) | 21 (1) | 20 (1) | 0 (1)  | -1 (1) | 2 (1)  |
| C (5)  | 19 (2) | 22 (1) | 27 (1) | -3 (1) | 0 (1)  | 1 (1)  |
| C (6)  | 16 (1) | 27 (2) | 27 (2) | 0 (1)  | 0 (1)  | 1 (1)  |
| C (7)  | 15 (2) | 28 (1) | 19 (1) | -1 (1) | -1 (1) | 3 (1)  |
| C (8)  | 18 (1) | 27 (1) | 22 (1) | 2 (1)  | 1 (1)  | 3 (1)  |
| C (9)  | 28 (2) | 26 (2) | 30 (2) | 5 (1)  | -3 (1) | 2 (1)  |
| C (10) | 20 (1) | 33 (2) | 21 (2) | 4 (1)  | 0 (1)  | 5 (1)  |
| C (11) | 18 (1) | 36 (2) | 17 (1) | -3 (1) | -1 (1) | -1 (1) |
| C (12) | 19 (1) | 26 (2) | 19 (1) | -2 (1) | -1 (1) | -1 (1) |
| C (13) | 19 (1) | 24 (1) | 19 (1) | 0 (1)  | -2 (1) | 2 (1)  |
| C (14) | 19 (1) | 30 (2) | 23 (1) | -3 (1) | -4 (1) | -2 (1) |
| C (15) | 26 (2) | 34 (2) | 24 (2) | -7 (1) | -1 (1) | -1 (1) |
| C (16) | 31 (2) | 31 (2) | 33 (2) | -9 (1) | -3 (1) | -1 (1) |
| C (17) | 30 (2) | 26 (2) | 40 (2) | 2 (1)  | -8 (1) | -2 (1) |
| C (18) | 26 (2) | 33 (2) | 30 (2) | 6 (1)  | 0 (1)  | -2 (1) |
| N      | 24 (1) | 31 (1) | 24 (1) | 2 (1)  | 1 (1)  | 1 (1)  |

Table A6 Hydrogen coordinates (  $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for k12cgf3.

|       | x    | y     | z    | U(eq) |
|-------|------|-------|------|-------|
| H(2)  | 2397 | 6796  | 7463 | 30    |
| H(3)  | 4679 | 5696  | 7038 | 30    |
| H(5)  | 1303 | 3189  | 6629 | 27    |
| H(6)  | -978 | 4291  | 7068 | 28    |
| H(9A) | 3485 | 4954  | 4506 | 42    |
| H(9B) | 5285 | 4808  | 4929 | 42    |
| H(9C) | 3566 | 5083  | 5384 | 42    |
| H(10) | 2645 | 3260  | 4028 | 30    |
| H(13) | 4037 | 1335  | 6178 | 25    |
| H(15) | 3967 | -640  | 4281 | 34    |
| H(16) | 3672 | -2544 | 4562 | 38    |
| H(17) | 2322 | -3052 | 5674 | 38    |
| H(18) | 1361 | -1676 | 6463 | 36    |

**4.32** 1,1'-Di(pyridin-1-yl)-2,2'-binaphthalene

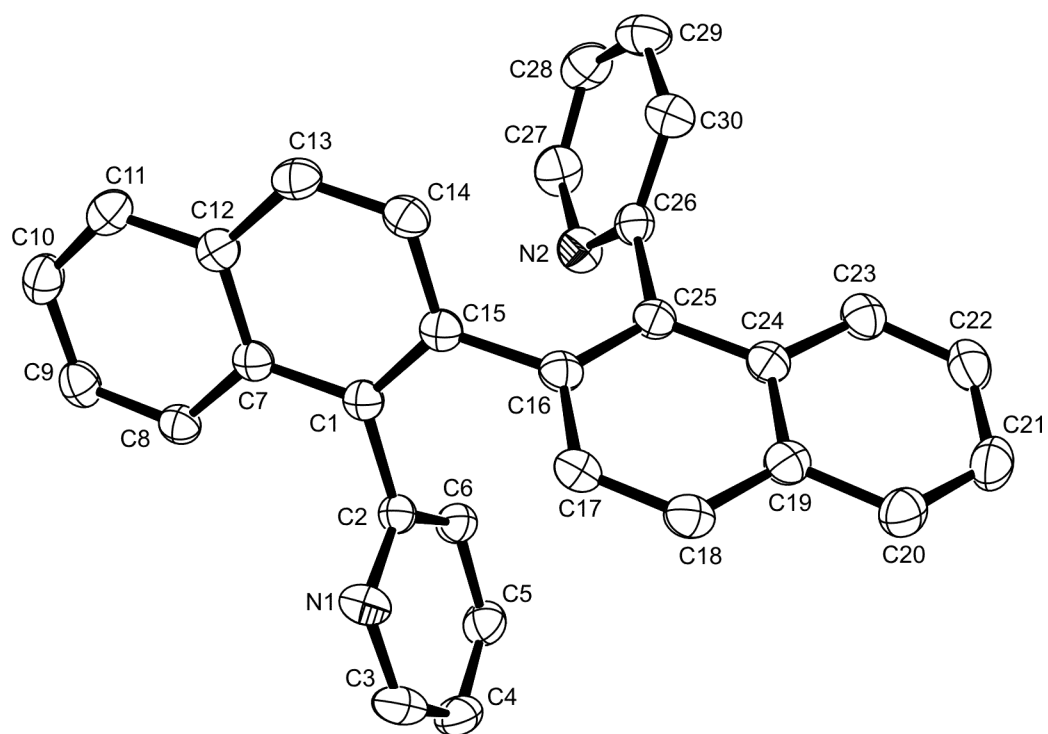


Table A13 Crystal data and structure refinement for h12cgf2.

|                                   |  |
|-----------------------------------|--|
| Identification code               | h12cgf2  |
| Empirical formula                 | C30 H20 N2   |
| Formula weight                    | 408.48   |
| Temperature                       | 150(2) K   |
| Wavelength                        | 0.71073 Å  |
| Crystal system, space group       | Monoclinic, $P 2_1/c$  |
| Unit cell dimensions              | a = 10.3941(3) Å $\alpha$ = 90 deg.<br>b = 16.1682(4) Å $\beta$ = 111.5911(14) deg.<br>c = 13.4782(4) Å $\gamma$ = 90 deg. |
| Volume                            | 2106.13(10) Å <sup>3</sup>   |
| Z, Calculated density             | 4, 1.288 Mg/m <sup>3</sup>   |
| Absorption coefficient            | 0.075 mm <sup>-1</sup>   |
| F(000)                            | 856  |
| Crystal size                      | 0.60 x 0.50 x 0.25 mm  |
| Theta range for data collection   | 4.12 to 27.47 deg.   |
| Limiting indices                  | -13 ≤ h ≤ 13, -20 ≤ k ≤ 20, -17 ≤ l ≤ 17   |
| Reflections collected / unique    | 36358 / 4807 [R(int) = 0.0703]   |
| Completeness to theta = 27.47     | 99.5 %   |
| Absorption correction             | Semi-empirical from equivalents  |
| Max. and min. transmission        | 0.9814 and 0.9562  |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>  |
| Data / restraints / parameters    | 4807 / 0 / 289   |
| Goodness-of-fit on F <sup>2</sup> | 1.041  |
| Final R indices [I > 2σ(I)]       | R1 = 0.0467, wR2 = 0.1027  |
| R indices (all data)              | R1 = 0.0838, wR2 = 0.1186  |
| Largest diff. peak and hole       | 0.198 and -0.255 e.Å <sup>-3</sup>   |



Table A14 Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf2.

U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x       | y        | z        | U (eq) |
|-------|---------|----------|----------|--------|
| N(1)  | 4534(1) | 2088(1)  | 3664(1)  | 31(1)  |
| N(2)  | 2705(1) | -1046(1) | 2655(1)  | 31(1)  |
| C(1)  | 2796(1) | 1080(1)  | 3626(1)  | 23(1)  |
| C(2)  | 4241(1) | 1284(1)  | 3729(1)  | 24(1)  |
| C(3)  | 5821(2) | 2266(1)  | 3717(1)  | 35(1)  |
| C(4)  | 6848(2) | 1683(1)  | 3874(1)  | 34(1)  |
| C(5)  | 6539(2) | 865(1)   | 3972(1)  | 32(1)  |
| C(6)  | 5211(1) | 659(1)   | 3880(1)  | 27(1)  |
| C(7)  | 2417(1) | 1157(1)  | 4539(1)  | 23(1)  |
| C(8)  | 3380(2) | 1390(1)  | 5557(1)  | 26(1)  |
| C(9)  | 2998(2) | 1436(1)  | 6423(1)  | 30(1)  |
| C(10) | 1626(2) | 1268(1)  | 6320(1)  | 33(1)  |
| C(11) | 670(2)  | 1043(1)  | 5351(1)  | 31(1)  |
| C(12) | 1034(1) | 968(1)   | 4443(1)  | 26(1)  |
| C(13) | 90(1)   | 696(1)   | 3440(1)  | 29(1)  |
| C(14) | 487(1)  | 598(1)   | 2590(1)  | 27(1)  |
| C(15) | 1855(1) | 788(1)   | 2669(1)  | 24(1)  |
| C(16) | 2247(1) | 702(1)   | 1714(1)  | 25(1)  |
| C(17) | 2637(1) | 1424(1)  | 1299(1)  | 27(1)  |
| C(18) | 3025(2) | 1389(1)  | 440(1)   | 29(1)  |
| C(19) | 3046(1) | 628(1)   | -67(1)   | 27(1)  |
| C(20) | 3510(2) | 581(1)   | -931(1)  | 33(1)  |
| C(21) | 3580(2) | -160(1)  | -1392(1) | 37(1)  |
| C(22) | 3161(2) | -887(1)  | -1025(1) | 34(1)  |
| C(23) | 2682(2) | -862(1)  | -207(1)  | 30(1)  |
| C(24) | 2626(1) | -107(1)  | 313(1)   | 25(1)  |
| C(25) | 2225(1) | -56(1)   | 1222(1)  | 24(1)  |
| C(26) | 1836(1) | -818(1)  | 1678(1)  | 25(1)  |
| C(27) | 2331(2) | -1700(1) | 3100(1)  | 37(1)  |
| C(28) | 1133(2) | -2146(1) | 2619(1)  | 38(1)  |
| C(29) | 263(2)  | -1917(1) | 1611(1)  | 38(1)  |
| C(30) | 622(2)  | -1244(1) | 1130(1)  | 32(1)  |

Table A15 Bond lengths [Å] for h12cgf2.

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|             |            |
|-------------|------------|
| N(1)-C(3)   | 1.3442(19) |
| N(1)-C(2)   | 1.3455(17) |
| N(2)-C(27)  | 1.3429(19) |
| N(2)-C(26)  | 1.3452(18) |
| C(1)-C(15)  | 1.3832(19) |
| C(1)-C(7)   | 1.4286(19) |
| C(1)-C(2)   | 1.4945(19) |
| C(2)-C(6)   | 1.3875(19) |
| C(3)-C(4)   | 1.380(2)   |
| C(3)-H(3)   | 0.9500     |
| C(4)-C(5)   | 1.380(2)   |
| C(4)-H(4)   | 0.9500     |
| C(5)-C(6)   | 1.380(2)   |
| C(5)-H(5)   | 0.9500     |
| C(6)-H(6)   | 0.9500     |
| C(7)-C(8)   | 1.4198(19) |
| C(7)-C(12)  | 1.4279(19) |
| C(8)-C(9)   | 1.365(2)   |
| C(8)-H(8)   | 0.9500     |
| C(9)-C(10)  | 1.408(2)   |
| C(9)-H(9)   | 0.9500     |
| C(10)-C(11) | 1.368(2)   |
| C(10)-H(10) | 0.9500     |
| C(11)-C(12) | 1.414(2)   |
| C(11)-H(11) | 0.9500     |
| C(12)-C(13) | 1.416(2)   |
| C(13)-C(14) | 1.363(2)   |
| C(13)-H(13) | 0.9500     |
| C(14)-C(15) | 1.4200(19) |
| C(14)-H(14) | 0.9500     |
| C(15)-C(16) | 1.4936(19) |
| C(16)-C(25) | 1.3888(19) |
| C(16)-C(17) | 1.4169(19) |
| C(17)-C(18) | 1.360(2)   |
| C(17)-H(17) | 0.9500     |
| C(18)-C(19) | 1.412(2)   |
| C(18)-H(18) | 0.9500     |
| C(19)-C(20) | 1.416(2)   |
| C(19)-C(24) | 1.4245(19) |
| C(20)-C(21) | 1.363(2)   |
| C(20)-H(20) | 0.9500     |
| C(21)-C(22) | 1.405(2)   |
| C(21)-H(21) | 0.9500     |
| C(22)-C(23) | 1.367(2)   |
| C(22)-H(22) | 0.9500     |
| C(23)-C(24) | 1.4197(19) |
| C(23)-H(23) | 0.9500     |
| C(24)-C(25) | 1.4342(19) |
| C(25)-C(26) | 1.4973(19) |
| C(26)-C(30) | 1.388(2)   |
| C(27)-C(28) | 1.377(2)   |
| C(27)-H(27) | 0.9500     |
| C(28)-C(29) | 1.377(2)   |
| C(28)-H(28) | 0.9500     |
| C(29)-C(30) | 1.386(2)   |
| C(29)-H(29) | 0.9500     |
| C(30)-H(30) | 0.9500     |

---

Table A16 Bond lengths [Å] and angles [deg] for h12cgf2.

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|                   |            |
|-------------------|------------|
| C(3)-N(1)-C(2)    | 116.62(12) |
| C(27)-N(2)-C(26)  | 116.93(13) |
| C(15)-C(1)-C(7)   | 120.59(12) |
| C(15)-C(1)-C(2)   | 120.20(12) |
| C(7)-C(1)-C(2)    | 119.15(12) |
| N(1)-C(2)-C(6)    | 122.87(13) |
| N(1)-C(2)-C(1)    | 116.80(12) |
| C(6)-C(2)-C(1)    | 120.33(12) |
| N(1)-C(3)-C(4)    | 124.08(13) |
| N(1)-C(3)-H(3)    | 118.0      |
| C(4)-C(3)-H(3)    | 118.0      |
| C(5)-C(4)-C(3)    | 118.39(13) |
| C(5)-C(4)-H(4)    | 120.8      |
| C(3)-C(4)-H(4)    | 120.8      |
| C(4)-C(5)-C(6)    | 118.84(14) |
| C(4)-C(5)-H(5)    | 120.6      |
| C(6)-C(5)-H(5)    | 120.6      |
| C(5)-C(6)-C(2)    | 119.13(13) |
| C(5)-C(6)-H(6)    | 120.4      |
| C(2)-C(6)-H(6)    | 120.4      |
| C(8)-C(7)-C(12)   | 118.23(13) |
| C(8)-C(7)-C(1)    | 122.42(12) |
| C(12)-C(7)-C(1)   | 119.32(12) |
| C(9)-C(8)-C(7)    | 121.09(13) |
| C(9)-C(8)-H(8)    | 119.5      |
| C(7)-C(8)-H(8)    | 119.5      |
| C(8)-C(9)-C(10)   | 120.56(14) |
| C(8)-C(9)-H(9)    | 119.7      |
| C(10)-C(9)-H(9)   | 119.7      |
| C(11)-C(10)-C(9)  | 119.95(14) |
| C(11)-C(10)-H(10) | 120.0      |
| C(9)-C(10)-H(10)  | 120.0      |
| C(10)-C(11)-C(12) | 121.15(14) |
| C(10)-C(11)-H(11) | 119.4      |
| C(12)-C(11)-H(11) | 119.4      |
| C(11)-C(12)-C(13) | 122.68(13) |
| C(11)-C(12)-C(7)  | 118.98(13) |
| C(13)-C(12)-C(7)  | 118.33(13) |
| C(14)-C(13)-C(12) | 121.36(13) |
| C(14)-C(13)-H(13) | 119.3      |
| C(12)-C(13)-H(13) | 119.3      |
| C(13)-C(14)-C(15) | 121.04(13) |
| C(13)-C(14)-H(14) | 119.5      |
| C(15)-C(14)-H(14) | 119.5      |
| C(1)-C(15)-C(14)  | 119.27(13) |
| C(1)-C(15)-C(16)  | 120.83(12) |
| C(14)-C(15)-C(16) | 119.86(12) |
| C(25)-C(16)-C(17) | 119.75(13) |
| C(25)-C(16)-C(15) | 122.14(12) |
| C(17)-C(16)-C(15) | 118.11(12) |
| C(18)-C(17)-C(16) | 121.28(13) |
| C(18)-C(17)-H(17) | 119.4      |
| C(16)-C(17)-H(17) | 119.4      |
| C(17)-C(18)-C(19) | 120.65(13) |
| C(17)-C(18)-H(18) | 119.7      |
| C(19)-C(18)-H(18) | 119.7      |
| C(18)-C(19)-C(20) | 121.00(13) |
| C(18)-C(19)-C(24) | 119.44(13) |
| C(20)-C(19)-C(24) | 119.54(13) |
| C(21)-C(20)-C(19) | 120.88(14) |

|                        |             |
|------------------------|-------------|
| C (21) -C (20) -H (20) | 119.6       |
| C (19) -C (20) -H (20) | 119.6       |
| C (20) -C (21) -C (22) | 119.91 (14) |
| C (20) -C (21) -H (21) | 120.0       |
| C (22) -C (21) -H (21) | 120.0       |
| C (23) -C (22) -C (21) | 120.77 (14) |
| C (23) -C (22) -H (22) | 119.6       |
| C (21) -C (22) -H (22) | 119.6       |
| C (22) -C (23) -C (24) | 121.12 (14) |
| C (22) -C (23) -H (23) | 119.4       |
| C (24) -C (23) -H (23) | 119.4       |
| C (23) -C (24) -C (19) | 117.73 (13) |
| C (23) -C (24) -C (25) | 123.27 (13) |
| C (19) -C (24) -C (25) | 118.94 (12) |
| C (16) -C (25) -C (24) | 119.90 (12) |
| C (16) -C (25) -C (26) | 119.36 (12) |
| C (24) -C (25) -C (26) | 120.69 (12) |
| N (2) -C (26) -C (30)  | 122.49 (13) |
| N (2) -C (26) -C (25)  | 116.16 (12) |
| C (30) -C (26) -C (25) | 121.32 (13) |
| N (2) -C (27) -C (28)  | 124.14 (15) |
| N (2) -C (27) -H (27)  | 117.9       |
| C (28) -C (27) -H (27) | 117.9       |
| C (27) -C (28) -C (29) | 118.47 (14) |
| C (27) -C (28) -H (28) | 120.8       |
| C (29) -C (28) -H (28) | 120.8       |
| C (28) -C (29) -C (30) | 118.70 (14) |
| C (28) -C (29) -H (29) | 120.7       |
| C (30) -C (29) -H (29) | 120.7       |
| C (29) -C (30) -C (26) | 119.26 (14) |
| C (29) -C (30) -H (30) | 120.4       |
| C (26) -C (30) -H (30) | 120.4       |

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Table A17 Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf2.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [ h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12} ]$$

|       | U11   | U22   | U33   | U23   | U13   | U12    |
|-------|-------|-------|-------|-------|-------|--------|
| N(1)  | 28(1) | 26(1) | 36(1) | 0(1)  | 8(1)  | -5(1)  |
| N(2)  | 35(1) | 30(1) | 27(1) | 3(1)  | 9(1)  | 1(1)   |
| C(1)  | 23(1) | 19(1) | 25(1) | 1(1)  | 9(1)  | 2(1)   |
| C(2)  | 26(1) | 25(1) | 20(1) | -1(1) | 9(1)  | -3(1)  |
| C(3)  | 33(1) | 30(1) | 37(1) | 2(1)  | 8(1)  | -11(1) |
| C(4)  | 25(1) | 44(1) | 33(1) | 0(1)  | 12(1) | -7(1)  |
| C(5)  | 27(1) | 37(1) | 33(1) | -2(1) | 13(1) | 1(1)   |
| C(6)  | 28(1) | 25(1) | 31(1) | 0(1)  | 13(1) | -1(1)  |
| C(7)  | 24(1) | 18(1) | 27(1) | 2(1)  | 9(1)  | 2(1)   |
| C(8)  | 28(1) | 22(1) | 28(1) | 0(1)  | 10(1) | -1(1)  |
| C(9)  | 38(1) | 27(1) | 24(1) | -1(1) | 10(1) | -1(1)  |
| C(10) | 42(1) | 33(1) | 30(1) | 1(1)  | 20(1) | 2(1)   |
| C(11) | 29(1) | 31(1) | 35(1) | 3(1)  | 16(1) | 3(1)   |
| C(12) | 26(1) | 22(1) | 30(1) | 3(1)  | 11(1) | 3(1)   |
| C(13) | 21(1) | 30(1) | 35(1) | 2(1)  | 9(1)  | 1(1)   |
| C(14) | 23(1) | 28(1) | 28(1) | -1(1) | 5(1)  | -1(1)  |
| C(15) | 26(1) | 20(1) | 26(1) | 2(1)  | 9(1)  | 2(1)   |
| C(16) | 21(1) | 27(1) | 23(1) | 1(1)  | 4(1)  | 0(1)   |
| C(17) | 27(1) | 24(1) | 28(1) | -1(1) | 7(1)  | -3(1)  |
| C(18) | 28(1) | 28(1) | 28(1) | 3(1)  | 7(1)  | -4(1)  |
| C(19) | 22(1) | 33(1) | 23(1) | 3(1)  | 4(1)  | 0(1)   |
| C(20) | 31(1) | 43(1) | 25(1) | 3(1)  | 9(1)  | -2(1)  |
| C(21) | 32(1) | 54(1) | 25(1) | -3(1) | 11(1) | 0(1)   |
| C(22) | 30(1) | 41(1) | 28(1) | -8(1) | 7(1)  | 2(1)   |
| C(23) | 26(1) | 33(1) | 27(1) | -1(1) | 6(1)  | 2(1)   |
| C(24) | 19(1) | 30(1) | 22(1) | 1(1)  | 3(1)  | 1(1)   |
| C(25) | 21(1) | 26(1) | 24(1) | 0(1)  | 5(1)  | 0(1)   |
| C(26) | 26(1) | 24(1) | 28(1) | -2(1) | 11(1) | 2(1)   |
| C(27) | 46(1) | 32(1) | 34(1) | 7(1)  | 14(1) | 3(1)   |
| C(28) | 46(1) | 26(1) | 50(1) | 8(1)  | 26(1) | 1(1)   |
| C(29) | 32(1) | 28(1) | 55(1) | -2(1) | 16(1) | -6(1)  |
| C(30) | 29(1) | 28(1) | 35(1) | -1(1) | 8(1)  | -1(1)  |

Table A18 Hydrogen coordinates (  $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for h12cgf2.

|       | x    | y     | z     | U(eq) |
|-------|------|-------|-------|-------|
| H(3)  | 6037 | 2828  | 3642  | 42    |
| H(4)  | 7745 | 1842  | 3914  | 40    |
| H(5)  | 7229 | 450   | 4100  | 38    |
| H(6)  | 4965 | 98    | 3919  | 33    |
| H(8)  | 4306 | 1517  | 5638  | 31    |
| H(9)  | 3664 | 1582  | 7099  | 36    |
| H(10) | 1364 | 1312  | 6923  | 40    |
| H(11) | -256 | 934   | 5288  | 37    |
| H(13) | -839 | 580   | 3359  | 35    |
| H(14) | -162 | 398   | 1933  | 33    |
| H(17) | 2627 | 1943  | 1627  | 33    |
| H(18) | 3285 | 1882  | 178   | 35    |
| H(20) | 3775 | 1072  | -1193 | 40    |
| H(21) | 3912 | -185  | -1960 | 44    |
| H(22) | 3210 | -1401 | -1349 | 41    |
| H(23) | 2382 | -1358 | 17    | 36    |
| H(27) | 2932 | -1867 | 3792  | 45    |
| H(28) | 912  | -2600 | 2973  | 46    |
| H(29) | -568 | -2214 | 1252  | 46    |
| H(30) | 43   | -1076 | 433   | 38    |

## Appendix 2

### List of publications

W. R. Reynolds, P. M. Liu, G. Kociok-Köhn and C. G. Frost, *Synlett*, 2013, **24**, 2687-2690

W. R. Reynolds and C. G. Frost, in *Palladium-Catalyzed Coupling Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 409-443. (Included in its entirety in Chapter 5)